SMIAdviser

A Clinical Support System for Serious Mental Illness

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Pharmacologic Considerations for ACT Team Prescribers: Focus on Clozapine and Long-Acting Injectable Antipsychotic Medications (LAIs)

ACT Provider Series – NW MHTTC and UW SPIRIT LAB

June 20, 2024

An APA and SAMHSA Initiative

AMERICAN PSYCHIATRIC ASSOCIATION

SAMHSA Substance Abuse and Mental Health Services Administration

CSS-SMI Initiative

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Disclosures

- Rob Cotes has received research funding (to institution) from Otsuka, Karuna, Roche, and Alkermes. He is a speaker and consultant to Saladax Biomedical and a speaker for Clinical Care Options.
- Donna Rolin has no disclosures.

Learning Objectives

- Discuss the advantages of early initiation of clozapine and long-acting injectable antipsychotic medications
- List three scenarios for when to obtain therapeutic drug monitoring for clozapine as per the ASCP/AGNP guideline.
- Describe three strategies for managing ongoing positive symptoms despite taking clozapine

Outline

SMI Adviser

LAIs

Clozapine

Monitoring and levels

Challenges

SMI Adviser

SMI Adviser Vision Statement

To transform care for people who have serious mental illness so they can live their best lives.

SMI Adviser is…

A national initiative that serves clinicians and providers across all mental heath practice settings

Focuses on the three most common conditions associated with serious mental illness: bipolar disorder, major depressive disorder, and schizophrenia

SMI Adviser offers…

Educational Opportunities

Vetted Resources

Consultations

Multiplatform content delivery

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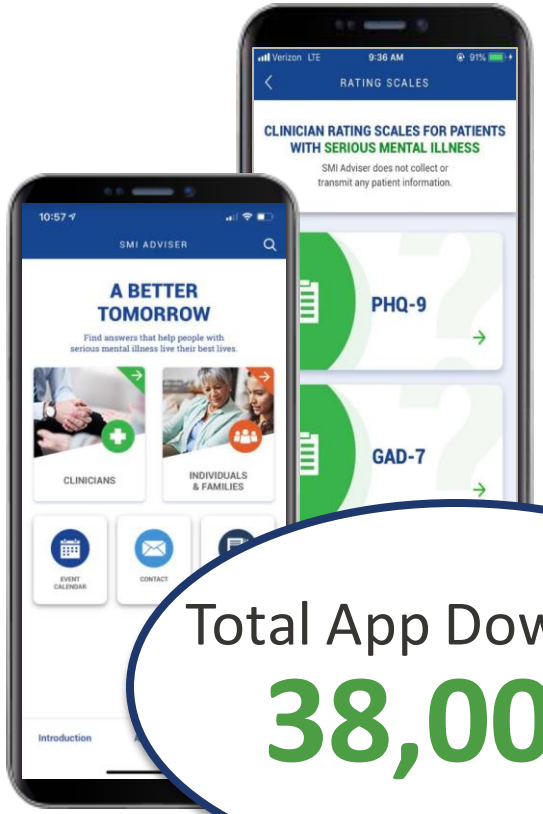

Total App Downloads

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Data as of March 26, 2024

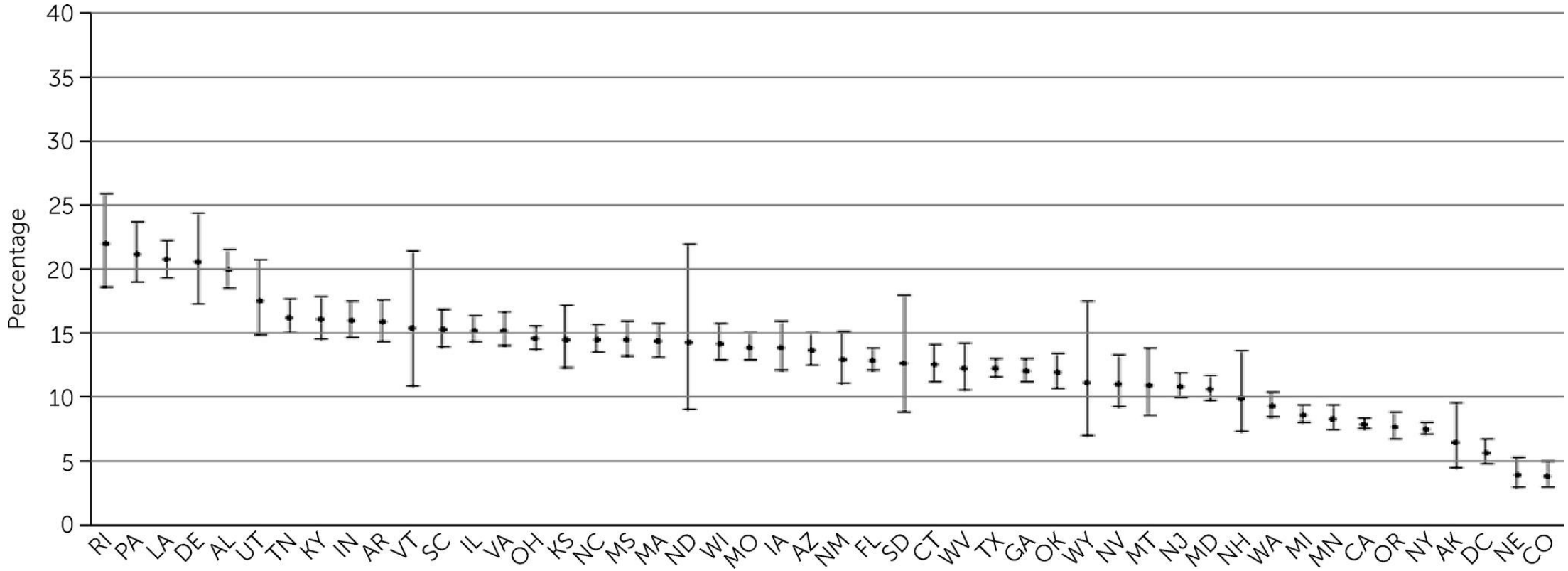
LAIs

APA Schizophrenia Guidelines (2020)

- APA suggests (2B) that patients receive treatment with a long-acting injectable antipsychotic medication if they prefer such treatment or if they have a history of poor or uncertain adherence.

LAI Utilization

State variation among Medicaid recipients ranged from 4-22%
Non-Hispanic Black patients more likely to receive LAI than Non-Hispanic White patients



Bareis N, Olfson M, Wall M, Stroup TS. Variation in Psychotropic Medication Prescription for Adults With Schizophrenia in theUnited States. Psychiatr Serv. 2022 May;73(5):492-500. doi: 10.1176/appi.ps.202000932. Epub 2021 Sep 30. PMID: 34587788; PMCID: PMC8964836.

LAIs versus orals, and versus themselves

- LAI Efficacy
  - In a meta-analysis of 25 observational studies, those on LAIs had lower odds of hospitalization (odds ratio 0.62, 95% CI 0.54-0.71) and fewer ED admissions (incidence rate ratio 0.86, 95% CI 0.77-0.97) compared to oral antipsychotics
- Real-world LAI performed better than LAIs in RCT
- LAI Comparative Efficacy
  - When comparing LAIs to LAIs, in a recent network meta-analysis which included 78 trials on 12 LAIs, LAI formulations of 1- and 3-month paliperidone, aripiprazole, and olanzapine had the highest effect sizes when assessing relapse prevention

Lin D, Thompson-Leduc P, Ghelerter I, Nguyen H, Lafeuille MH, Benson C, Mavros P, Lefebvre P. Real-World Evidence of the Clinical and Economic Impact of Long-Acting Injectable Versus Oral Antipsychotics Among Patients with Schizophrenia in the United States: A Systematic Review and Meta-Analysis. CNS Drugs. 2021 May;35(5):469-481. doi: 10.1007/s40263-021-00815-y. Epub 2021 Apr 28. Erratum in: CNS Drugs. 2021 Aug;35(8):923. PMID: 33909272; PMCID: PMC8144083.; Efthimiou O, Taipale H, Radua J, Schneider-Thoma J, Pinzón-Espinosa J, Ortuño M, Vinkers CH, Mittendorfer-Rutz E, Cardoner N, Tanskanen A, Fusar-Poli P, Cipriani A, Vieta E, Leucht S, Tiihonen J, Luykx JJ. Efficacy and effectiveness of antipsychotics in schizophrenia: network meta-analyses combining evidence from randomised controlled trials and real-world data. Lancet Psychiatry. 2024 Feb;11(2):102-111. doi: 10.1016/S2215-0366(23)00366-8. Epub 2024 Jan 9. PMID: 38215784.Ostuzzi G, Bertolini F, Del Giovane C, Tedeschi F, Bovo C, Gastaldon C, Nosé M, Ogheri F, Papola D, Purgato M, Turrini G, Correll CU, Barbui C. Maintenance Treatment With Long-Acting Injectable Antipsychotics for People With Nonaffective Psychoses: A Network Meta-Analysis. Am J Psychiatry. 2021 May 1;178(5):424-436. doi: 10.1176/appi.ajp.2020.20071120. Epub 2021 Feb 18. PMID: 33596679.

PRELAPSE Study

- Study design
  - Early psychosis patients (18-35 with < 5 years of antipsychotic exposure)
  - Cluster randomized design, 39 mental health centers
  - Long acting-aripiprazole versus clinicians choice
- Results
  - Only 14.4% refused to participate they would not consider an LAI
  - NNT of 7 to prevent 1 hospitalization when comparing LAI to clinician's choice

Kane JM, Schooler NR, Marcy P, Correll CU, Achtyes ED, Gibbons RD, Robinson DG. Effect of Long-Acting Injectable Antipsychotics vs Usual Care on Time to First Hospitalization in Early-Phase Schizophrenia: A Randomized Clinical Trial. JAMA Psychiatry. 2020 Dec 1;77(12):1217-1224. doi: 10.1001/jamapsychiatry.2020.2076. Erratum in: JAMA Psychiatry. 2020 Dec 1;77(12):1310. PMID: 32667636; PMCID: PMC7364341.; Kane JM, Schooler NR, Marcy P, Achtyes ED, Correll CU, Robinson DG. Patients With Early-Phase Schizophrenia Will Accept Treatment With Sustained-Release Medication (Long-Acting Injectable Antipsychotics): Results From the Recruitment Phase of the PRELAPSE Trial. J Clin Psychiatry. 2019 Apr 23;80(3):18m12546. doi: 10.4088/JCP.18m12546. PMID: 31050233.

New LAI Options (Since 2021)

Medication	FDA approval	Indication	Site	Dosage (mg)	Notable Characteristics
Abilify Asimtufii (aripiprazole extended-release suspension)	4/2023	SCZ, BP1	Gluteal IM	720, 920	May take 2 weeks to fully assess oral tolerability, 14-day oral supplementation, given q 8 weeks
Invega Hafyera (paliperidone 6-mo LAI)	8/2021	SCZ	Gluteal IM	1092, 1560	Administer after 4 months of Sustenna or 1 month of Trinza, given q 6 month
Rykindo (risperidone for extended-release suspension)	1/2023	SCZ, BP1	Gluteal IM	12.5, 25, 37.5, 50	7-day oral supplementation (21 days for Consta), given q2 weeks
Uzedy (risperidone for extended-release suspension)	4/2023	SCZ	Abdomen or upper arm SC	50, 75, 100, 125, 150, 200, 250	Oral overlap not required, given q1 or q2 months

Management of Breakthrough Symptoms

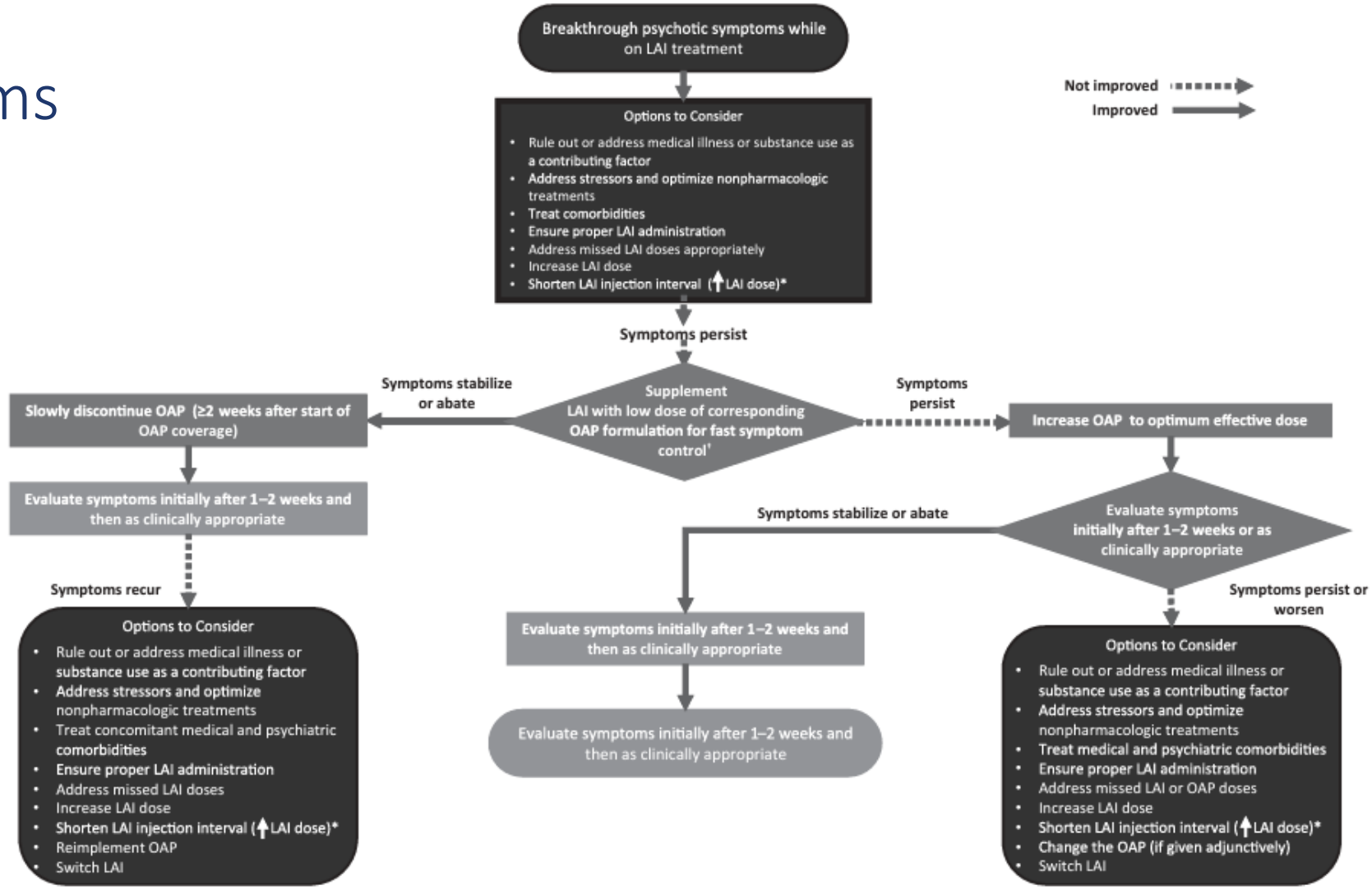


FIGURE 1. Management of breakthrough psychotic symptoms in a patient receiving long-acting injectable (LAI) antipsychotic in whom the LAI antipsychotic dose has been optimized. LAI = long-acting injectable; OAP = oral antipsychotic. *Off-label; based on PK modeling (no supporting clinical trial data available).[17] †Caution should be exercised with this strategy, because data on the safety of concomitant use of LAI and oral antipsychotics are limited, especially over extended periods of time.

Correll CU, Sliwa JK, Najarian DM, Saklad SR. Practical considerations for managing breakthrough psychosis and symptomatic worsening in patients with schizophrenia on long-acting injectable antipsychotics. CNS Spectr. 2019 Aug;24(4):354-370. doi: 10.1017/S1092852918001098. Epub 2018 Dec 27. PMID: 30587268.

SMI Adviser LAI Tools for Clinicians

LAI Conversion Tool

This tool is designed to provide dosing recommendations for initial and maintenance doses of long-acting injectable antipsychotic medications based on an oral dose of antipsychotic medication.

Oral tolerability with all medications should be verified prior to consideration of a long-acting injectable antipsychotic medication.

Select the current oral medication and oral dose that the patient is receiving. The LAI dosing recommendations will populate with links to additional tips on the corresponding long-acting injectable antipsychotic medication.

PO Med *(Required)*

Paliperidone

PO Dose *(Required)*

6 mg

LAI Med and Dose

Initial Dose:

- 234 mg Invega Sustenna on day 1 and 156 mg Invega Sustenna on day 8. Maintenance dose is given 5 weeks after first dose.

Maintenance Dose:

- 117 mg Invega Sustenna every 4 weeks
- 410 mg Invega Trinza every 12 weeks (Stabilization with at least 4 months [4 injections] of Invega Sustenna required prior to initiation of Invega Trinza)

smiadviser.org/lai-conversion-tool#

LAI Explorer

This tool is designed to provide knowledge for utilization of a long-acting injectable (LAI) medication based upon the selection by the provider. The filters on the left side of the tool provide the opportunity to select characteristics of the available LAI medications to review available LAIs which meet those criteria.

Oral tolerability with all medications should be verified prior to consideration of a long-acting injectable antipsychotic medication.

howing 12 results

Indication(s)

- Bipolar I Maintenance
- Schizoaffective Disorder
- Schizophrenia

Generic Drug Name

- Aripiprazole
- Fluphenazine
- Haloperidol
- Olanzapine
- Paliperidone
- Risperidone

Maintenance Injection Site(s)

Maintenance Injection Interval

Storage

Oral Overlap

Loading Dose

Reconstitution

REMS

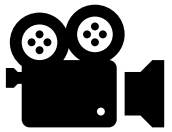
Abilify Asimtufii	Abilify Maintena	Aristada	Fluphenazine Decanoate
Haloperidol Decanoate	Invega Hafyera	Invega Sustenna	Invega Trinza
Perseris	Risperdal Consta	Uzedy	Zyprexa Relprevv

smiadviser.org/lai-explorer

Clozapine

APA Guidelines and Clozapine

- Recommends clozapine after “minimal or no response to **two** trials of antipsychotic medication”
- Recommends that patients with schizophrenia be treated with clozapine if the risk for suicide attempts or suicide remains substantial despite other treatments.
- Suggests that patients with schizophrenia be treated with clozapine if the risk for aggressive behavior remains substantial despite other treatments.



Webinar on Clozapine Pharmacodynamics and Pharmacokinetics, by Dr. Cotes https://education.smiadviser.org/diweb/catalog/item?id=8194965

Tip on talking to your patient about clozapine: https://smiadviser.org/knowledge_post/how-do-you-present-clozapine-to-a-person-who-might-benefit-from-it

American Psychiatric Association. (2020). "The American Psychiatric Association Practice Guideline for the Treatment of Patients with Schizophrenia, Third Edition." from https://www.psychiatry.org/psychiatrists/practice/clinical-practice-guidelines.

Treatment Resistant Schizophrenia (TRS)

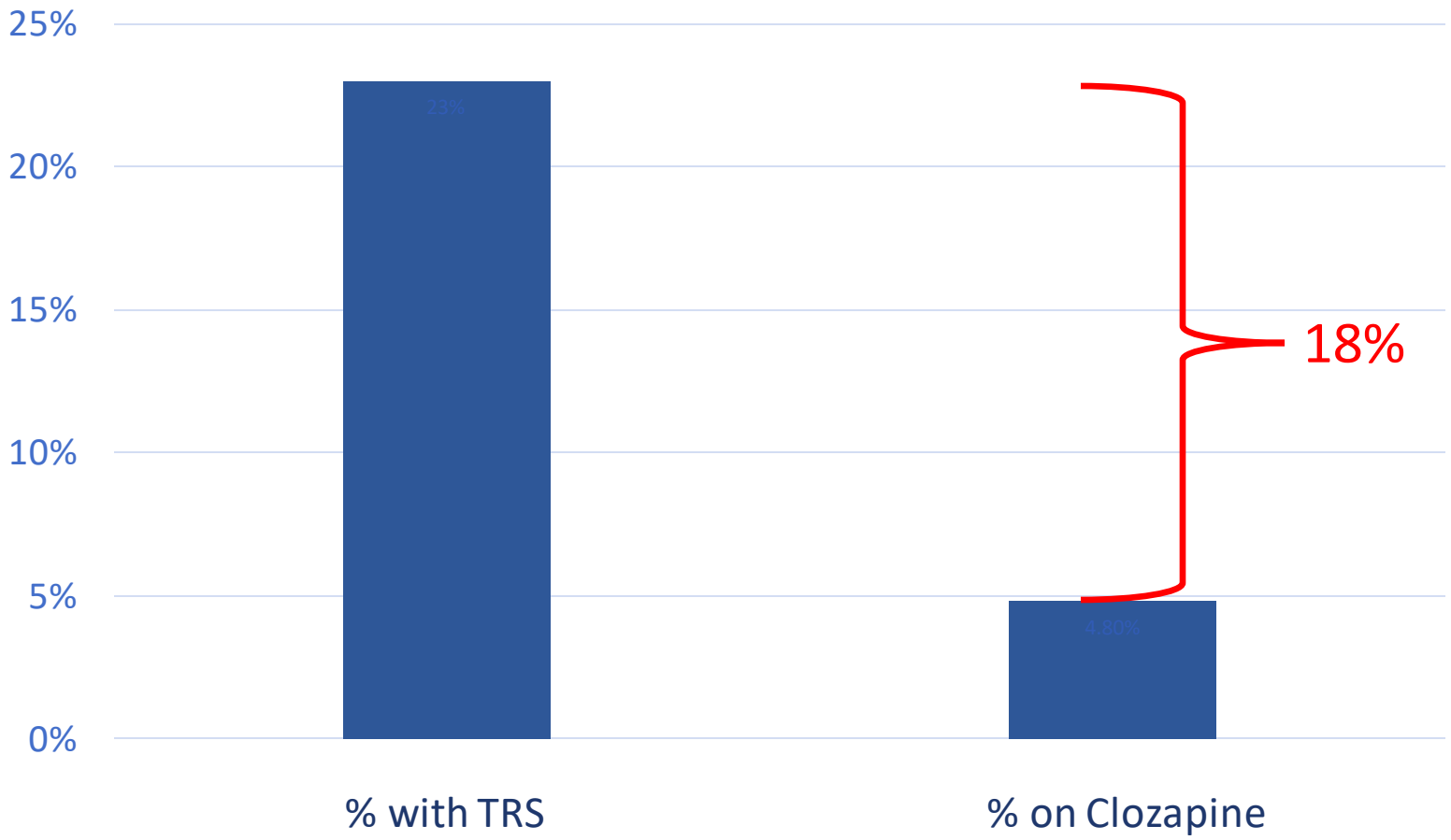
- Causes considerable suffering, including 34 billion dollars in direct medical costs to the US
- High rate of suicidal ideation (44%)
- High rates of smoking (56%) and substance abuse (51%)
- **Rate of TRS was 23% among first-episode cohorts in a recent meta-analysis including 12 studies**

Kennedy, J. L., Altar, C. A., Taylor, D. L., Degtiar, I., & Hornberger, J. C. (2014). The social and economic burden of treatment-resistant schizophrenia: a systematic literature review. *Int Clin Psychopharmacol, 29*(2), 63-76. Conley, R. R., & Kelly, D. L. (2001). Management of treatment resistance in schizophrenia. *Biol Psychiatry, 50*(11), 898-911. Kisely, S. (2022). Rates of treatment-resistant schizophrenia from first-episode cohorts: systematic review and meta-analysis. *Br J Psychiatry, 220*(3), 115-120.

Clozapine efficacy

- Response rate for TRS (Brunton, 2018)
  - 0% typical antipsychotics
  - 10% atypical antipsychotics
  - 40-60% clozapine
- Meta-analysis 21 studies (Siskind et al., 2016)
  - Clozapine superior efficacy for TRS for positive symptoms in the short-term and long-term
- Preferred by patients over other antipsychotics 54-86% (Parkes et al., 2022, Cotes et al., 2021)

US Clozapine Underutilization Gap



Importance of early clozapine initiation

- Fewer antipsychotic trials and psychiatric hospitalizations
- Minimizing the delay initiating clozapine after onset of TRS
  - Delay <2.8 years = response 81.6%
  - Delay >2.8 years = response 30.8%

Nielsen J, Nielsen RE, Correll CU. Predictors of clozapine response in patients with treatment-refractory schizophrenia: results from a Danish Register Study. *J Clin Psychopharmacol.* 2012;32(5):678-683. Yoshimura B, Yada Y, So R, Takaki M, Yamada N. The critical treatment window of clozapine in treatment-resistant schizophrenia: Secondary analysis of an observational study. Psychiatry Res. 2017 Apr;250:65-70. doi: 10.1016/j.psychres.2017.01.064. Epub 2017 Jan 24. PMID: 28142068.

Tips for Identifying TRS patients

- Can be difficult to untangle TRS from a lack of adherence
- Look for persistent positive symptoms on LAIs
- Some TRS patients are very sensitive to EPS from conventional D2 blockers
- Young age of onset is one of the most common predictors of TRS
- TRS is more likely to occur immediately after onset of symptoms, but can develop over time

Smart SE, Kępińska AP, Murray RM, MacCabe JH. Predictors of treatment resistant schizophrenia: a systematic review of prospective observational studies. Psychol Med. 2021 Jan;51(1):44-53. doi: 10.1017/S0033291719002083. Epub 2019 Aug 29. PMID: 31462334; PMCID: PMC7856410.

Clozapine and Suicide

- Schizophrenia lifetime risk of suicide 4.9%
- Clozapine was associated with less suicidal behavior and suicide attempts than olanzapine in the InterSePT study
- In a study combining a Swedish and Finnish registry
  - Clozapine only antipsychotic associated with decreased risk of suicide
  - Clozapine HR 0.64-0.66
  - BZD and Z-drugs associated with increased risk (HR 1.29-1.30, 1.33-1.62, respectively)

Palmer, B. A., Pankratz, V. S., & Bostwick, J. M. (2005). The lifetime risk of suicide in schizophrenia: a reexamination. *Arch Gen Psychiatry, 62*(3), 247-253. doi:10.1001/archpsyc.62.3.247

Meltzer, H. Y., Alphs, L., Green, A. I., Altamura, A. C., Anand, R., Bertoldi, A., . . . Potkin, S. (2003). Clozapine treatment for suicidality in schizophrenia: International Suicide Prevention Trial (InterSePT). *Arch Gen Psychiatry, 60*(1), 82-91. doi:10.1001/archpsyc.60.1.82

Taipale, H., Lähteenvuo, M., Tanskanen, A., Mittendorfer-Rutz, E., & Tiihonen, J. (2020). Comparative Effectiveness of Antipsychotics for Risk of Attempted or Completed Suicide Among Persons With Schizophrenia. *Schizophrenia Bulletin, 47*(1), 23-30. doi:10.1093/schbul/sbaa111

Protective effect of clozapine on suicide

- Statewide autopsy reports from the Maryland Office of the Chief Medical Examiner
- Decedents were more likely to die via suicide when olanzapine was detected in the blood when compared to clozapine
- OR = 0.47, P = .011

Manner of Death	Olanzapine (n=571)	Clozapine (n=50)	Total (n=621)
Accident	163 (29%)	23 (46%)	186 (30%)
Likely suicide	408 (71%)	27 (54%)	435 (70%)

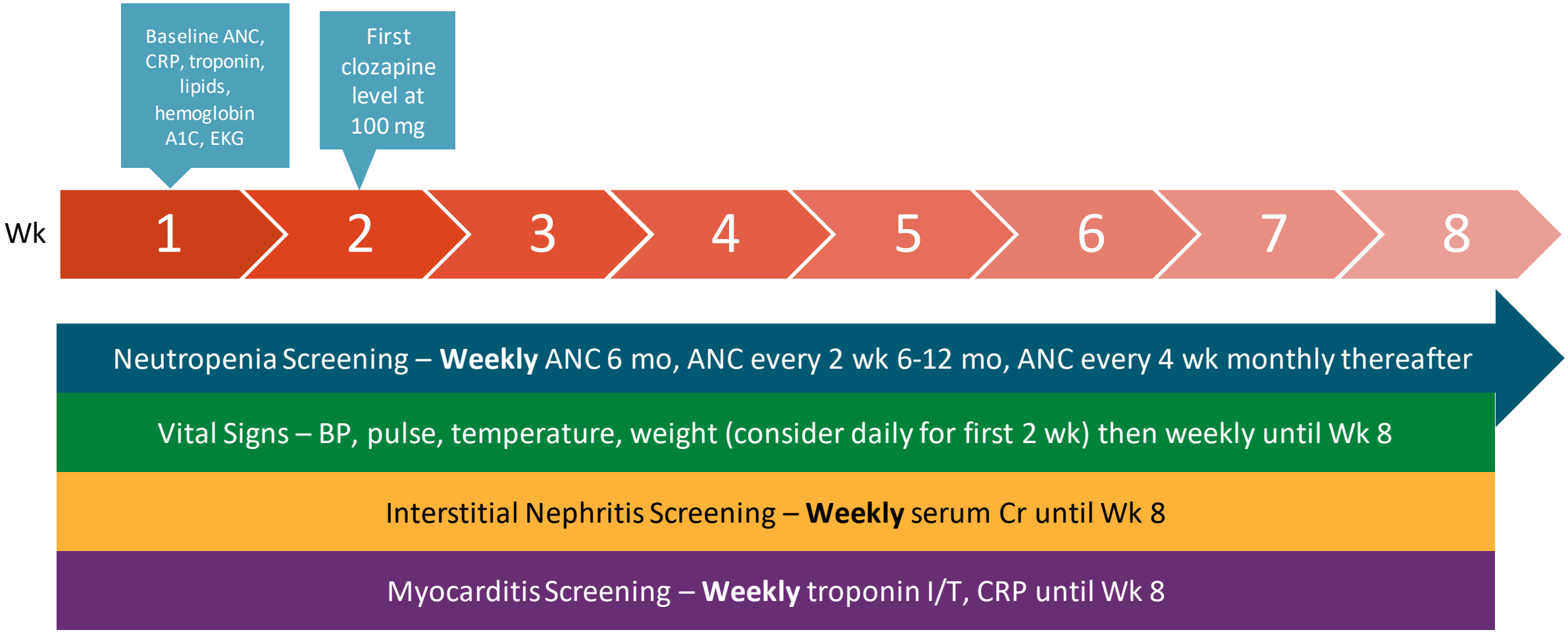
Violence, Schizophrenia, and Clozapine

- Physically assaultive schizophrenia patients randomized to CLO, OLZ, or HAL (N=99)
  - Clozapine superior to OLZ and HAL in reducing assaults
  - For conduct disorder patients specifically (N=53), clozapine was:
    - 4X more likely to result in lower violence than HAL
    - 3X more likely to result in lower violence than OLZ
- REVISIT-C study currently in progress

Krakowski, M., Tural, U., & Czobor, P. (2021). The Importance of Conduct Disorder in the Treatment of Violence in Schizophrenia: Efficacy of Clozapine Compared With Olanzapine and Haloperidol. *Am J Psychiatry*, appiajp202020010052.

Monitoring and Levels

Initial Monitoring



Correll. CNS Drugs. 2022;36:659.

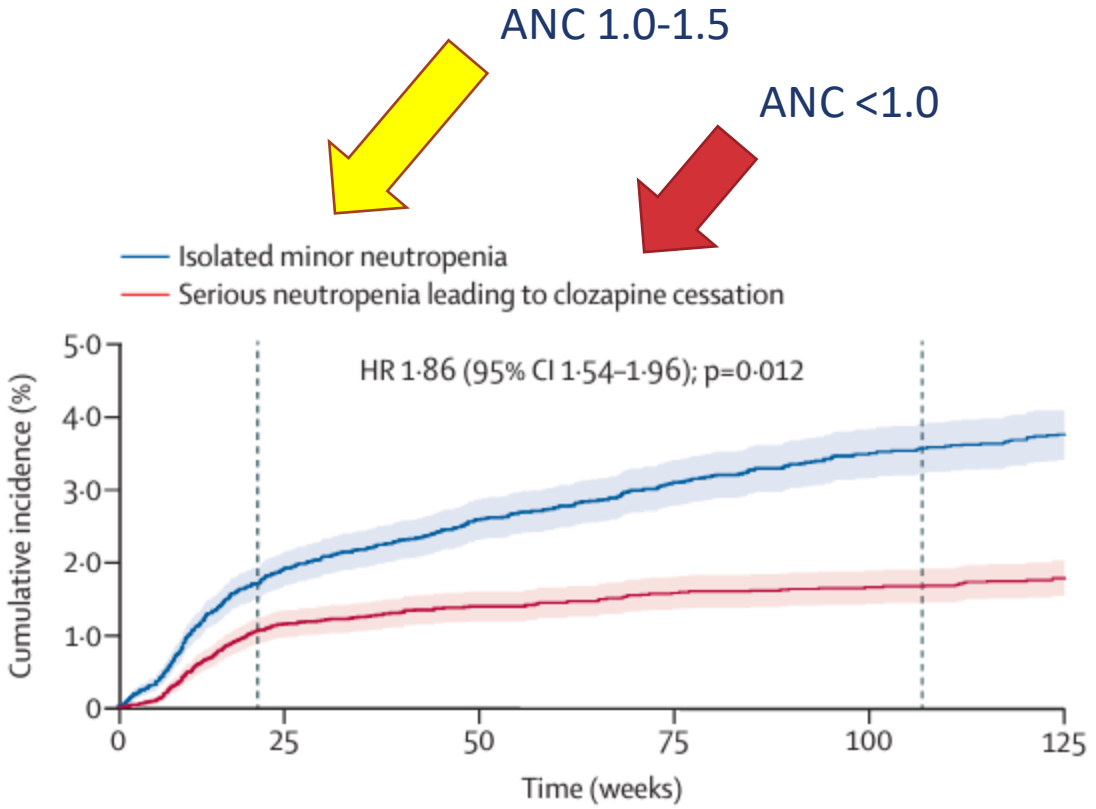
Neutropenia Meta-Analysis

- Mechanism: unclear, possibly-immune mediated rather than direct bone marrow toxicity
- ANC weekly first 6 mo, q2 weeks mo 6-12, monthly at 12 months
- 3.8% neutropenia
- 0.9% severe neutropenia
- 0.013% death due to neutropenia (1/7700)
- Peak incidence 1 month after initiation
- 89% cases severe neutropenia occurred at 1 year

Myles, N., Myles, H., Xia, S., Large, M., Kisely, S., Galletly, C., . . . Siskind, D. (2018). Meta-analysis examining the epidemiology of clozapine-associated neutropenia. *Acta Psychiatr Scand, 138*(2), 101-109. doi:10.1111/acps.12898

Key Neutropenia Studies

- Sample: Viatris clozapine patient monitoring system (CPMS) in Australia and New Zealand from 1990-2022
- Used data from 26,630 people with 2.6 MM ANCs
- Median time until serious neutropenic event was 17 weeks
- Risk of serious neutropenia at 2 years became negligible



Northwood K, Myles N, Clark SR, Every-Palmer S, Myles H, Kisely S, Warren N, Siskind D. Evaluating the epidemiology of clozapine-associated neutropenia among people on clozapine across Australia and Aotearoa New Zealand: a retrospective cohort study. The Lancet Psychiatry. 2024;11(1):27-35. doi: https://doi.org/10.1016/S2215-0366(23)00343-7.

Key Neutropenia Studies

- Prospective, multinational (US and Nigeria) study
- 274 participants enrolled and 227 completed six months of clozapine
  - 80% ACKR-null genotype
- 25% of patients had an ANC < 1.5
  - Observed one case of severe neutropenia

Kelly DL, Glassman M, Wonodi I, Vyas G, Richardson CM, Nwulia E, Wehring HJ, Oduguwa T, Mackowick M, Hipolito MMS, Peters O, Rai N, Park J, Adebayo AO, Gorelick DA, Weiner E, Liu F, Kearns AM, Adams HA, Love RC, Chen S, Olaniyan A, Ambulos N, McKoy D, Nallani MC, Lanzkron S, Mengistab M, Barr B, Davis E, Lawal R, Buchanan RW, Adebayo R. Clozapine and neutrophil response in patients of African descent: A six-month, multinational, prospective, open-label clinical trial. Schizophr Res. 2023 Aug 24:S0920-9964(23)00260-8. doi: 10.1016/j.schres.2023.08.002. Epub ahead of print. PMID: 37633776.

Changes to Clozapine REMS

- November 15, 2021 – New Clozapine REMS went into effect
- November 19, 2021 – Certain provisions of REMS were suspended including the need for the pharmacist to have a REMS authorization dispense form
- February 17, 2022 – Temporary suspension extended
- November 2, 2022 – Inpatient pharmacies may dispense a supply of clozapine that aligns with the patient's monitoring frequency

CLOZAPINE REMS

Where are things with REMS?

Latest Update

September 21, 2023 - As part of our regular review of all risk evaluation and mitigation strategies (REMS), and in light of the Agency's continued exercise of enforcement discretion with respect to certain aspects of the Clozapine REMS, FDA is conducting a thorough reevaluation of the Clozapine REMS to determine whether the REMS can be modified to minimize burden on patients, pharmacies, and prescribers while maintaining safe use of clozapine.

- Three Studies
  - Brigham and Women's Hospital to include an analysis of clozapine utilization and adherence to REMS requirements for ANC and clinical outcomes
  - VA study to understand incidence and severity of neutropenia
  - Sentinel System study to understand adherence to monitoring requirements
- "The Agency intends to take appropriate regulatory action, as needed, based on its reevaluation of the Clozapine REMS"

POC ANC testing

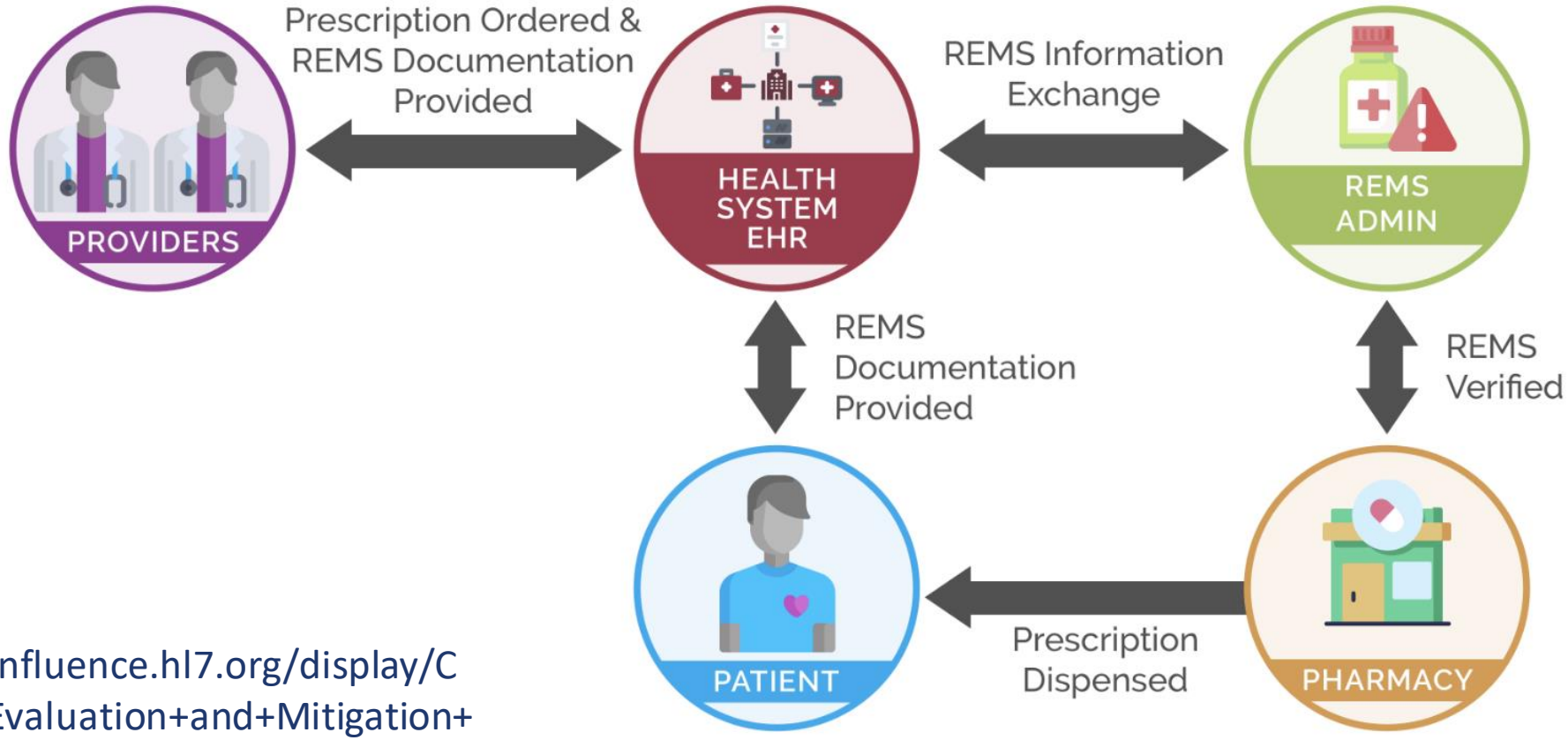
- FDA Approved, CLIA-waived device
  Uses 28-gauge lancet for fingersticks
- Device can be placed in the clinic, mobile team, or at the patient's home
- Automatically uploads results to REMS

Kelly D, Glassman M, Mackowick M, Park J, Navarro-De La Vega M, Wehring H, Vyas G, Richardson C. O9.1. Satisfaction with using a novel fingerstick for absolute neutrophil count (ANC) at the point of treatment in patients treated with clozapine. Schizophrenia Bulletin. 2020;46:S20-S21.

POC ANC Logistics, Advantages, and Disadvantages

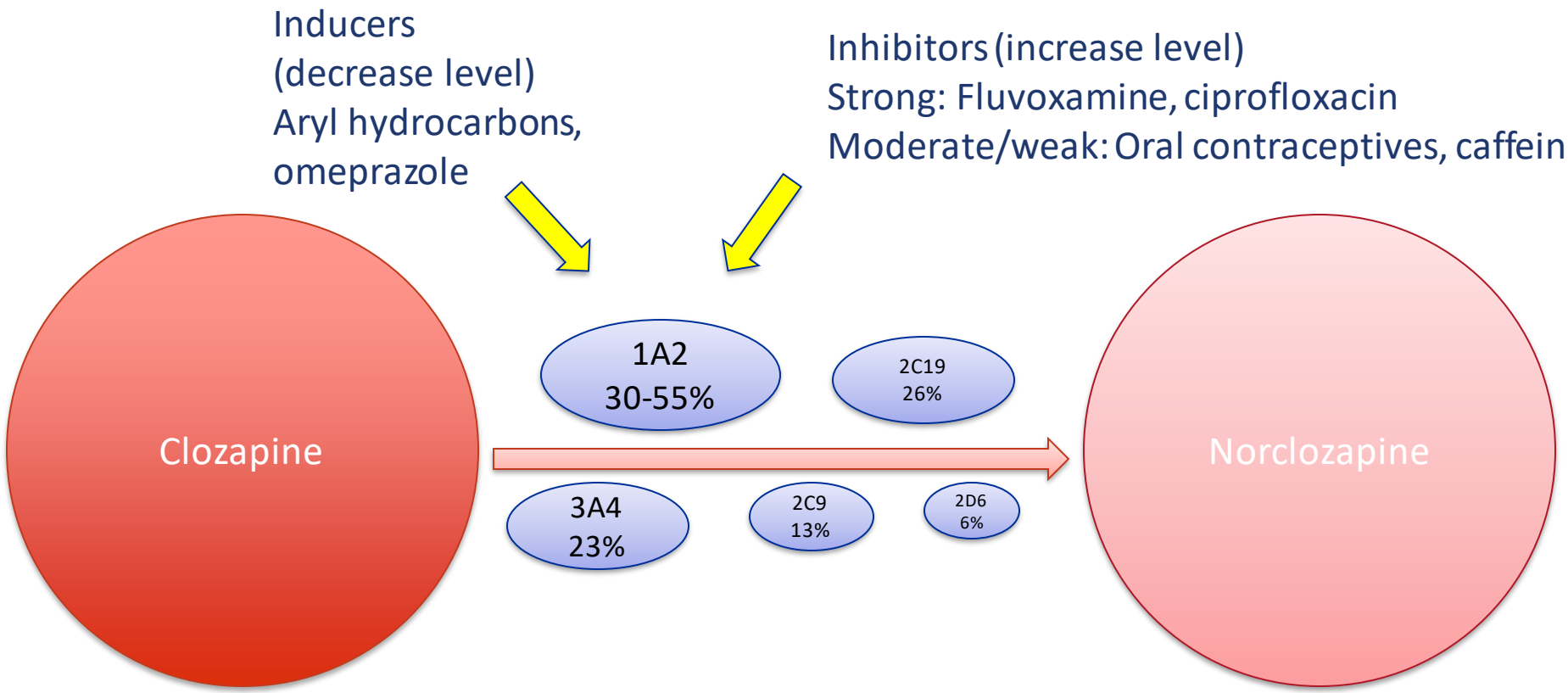
- Available in clinic (Athelas One) or home (Athelas Home)
- Advantages
  - Can expand clozapine access
  - Results typically back in 3 minutes or less
- Disadvantages
  - Sometimes venipuncture is still needed

Possible solution: HL7 CodeX FHIR Accelerator Community



https://confluence.hl7.org/display/COD/Risk+Evaluation+and+Mitigation+Strategies+%28REMS%29+Integration

Relative Contribution of CYP Enzymes to Biotransformation



Meyer JM, Stahl SM (2019). The Clozapine Handbook: Stahl's Handbooks, Cambridge University Press.

Antipsychotics for which TDM is “strongly recommended”

- **Clozapine**
- Fluphenazine
- Haloperidol
- Olanzapine
- Perazine
- Perphenazine

Schoretsanitis G, Kane JM, Correll CU, Marder SR, Citrome L, Newcomer JW, Robinson DG, Goff DC, Kelly DL, Freudenreich O, Piacentino D, Paulzen M, Conca A, Zernig G, Haen E, Baumann P, Hiemke C, Gründer G; American Society of Clinical Psychopharmacology, Pharmakopsychiatrie TTDMTFOTAFNU. Blood Levels to Optimize Antipsychotic Treatment in Clinical Practice: A Joint Consensus Statement of the American Society of Clinical Psychopharmacology and the Therapeutic Drug Monitoring Task Force of the Arbeitsgemeinschaft für Neuropsychopharmakologie und Pharmakopsychiatrie. J Clin Psychiatry. 2020 May 19;81(3):19cs13169. doi: 10.4088/JCP.19cs13169. PMID: 32433836.

ASCP/AGNP TDM may be valuable in the following situations:

- Uncertain adherence
- Lack of response within established dose ranges
- Symptom recurrence during maintenance tx
- Adverse drug reactions
- Combination tx with inducers or inhibitors
- Certain ancestral heritage
- High or low body weight
- Special populations (pregnant, children, elderly)
- Pts with intellectual disability
- Forensic patients
- Hepatic or renal dysfunction
- Acute of chronic inflammatory conditions
- Post-operative care for restrictive GI resection
- Switching from original preparations to generics
- Switching from between oral to LAI agents

Schoretsanitis G, Kane JM, Correll CU, Marder SR, Citrome L, Newcomer JW, Robinson DG, Goff DC, Kelly DL, Freudenreich O, Piacentino D, Paulzen M, Conca A, Zernig G, Haen E, Baumann P, Hiemke C, Gründer G; American Society of Clinical Psychopharmacology, Pharmakopsychiatrie TTDMTFOTAFNU. Blood Levels to Optimize Antipsychotic Treatment in Clinical Practice: A Joint Consensus Statement of the American Society of Clinical Psychopharmacology and the Therapeutic Drug Monitoring Task Force of the Arbeitsgemeinschaft für Neuropsychopharmakologie und Pharmakopsychiatrie. J Clin Psychiatry. 2020 May 19;81(3):19cs13169. doi: 10.4088/JCP.19cs13169. PMID: 32433836.

Clozapine Levels

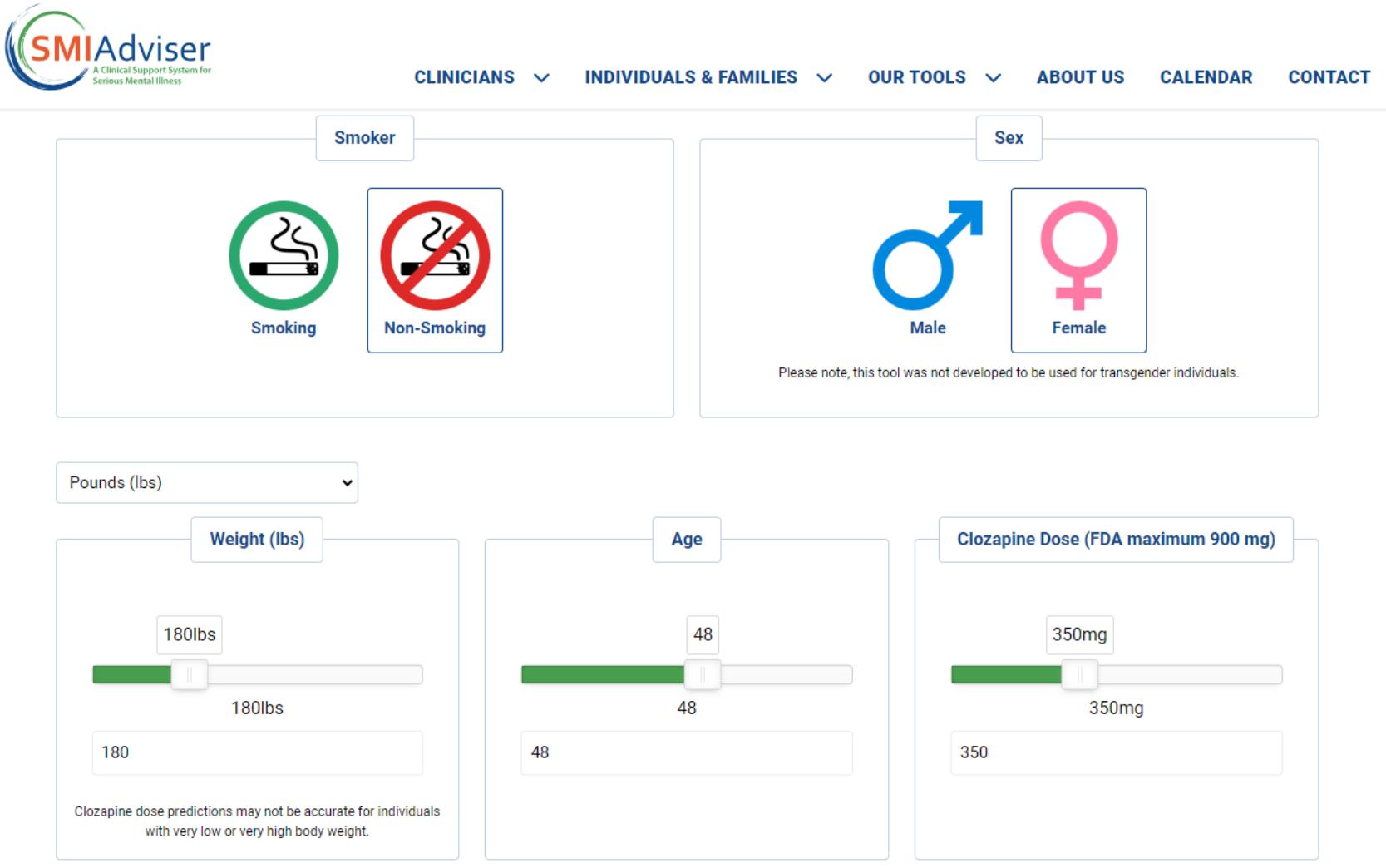
- AGNP guidelines reference range 350 – 600 ng/mL
- Risk of ADRs increase at levels above 1000 ng/mL
- Other sources indicate levels up to 1000 are not unsafe and should be pursued in non-responders

Rostami-Hodjegan, A., Amin, A. M., Spencer, E. P., Lennard, M. S., Tucker, G. T., & Flanagan, R. J. (2004). Influence of dose, cigarette smoking, age, sex, and metabolic activity on plasma clozapine concentrations: a predictive model and nomograms to aid clozapine dose adjustment and to assess compliance in individual patients. *J Clin Psychopharmacol, 24*(1), 70-78. doi:10.1097/01.jcp.0000106221.36344.4d. Yada Y, Kitagawa K, Sakamoto S, et al: The relationship between plasma clozapine concentration and clinical outcome: a cross-sectional study. Acta Psychiatr Scand 143:227-237, 2021

Concentration/Dose Relationships

Sex/smoking status	Concentration/Dose	Dose expected to reach 350 ng/mL
Female smoker	0.80	435 mg/d
Female nonsmoker	1.32	265 mg/d
Male smoker	0.67	525 mg/d
Male nonsmoker	1.08	325 mg/d

Meyer JM, Stahl SM (2021). The Clinical Use of Antipsychotic Plasma Levels: Stahl's Handbooks. Cambridge, Cambridge University Press.
Schoretsanitis G, Kane JM, Correll CU, et al: Blood Levels to Optimize Antipsychotic Treatment in Clinical Practice: A Joint Consensus Statement of the American Society of Clinical Psychopharmacology and the Therapeutic Drug Monitoring Task Force of the Arbeitsgemeinschaft für Neuropsychopharmakologie und Pharmakopsychiatrie. J Clin Psychiatry 81, 2020



https://smiadviser.org/clozapine-dose-planner

Interpreting MR ratio

Expected value
for nonsmokers

<1.0 | 1.3 | >1.7 | >3.0

+ Inducer (smoking, carbamazepine, omeprazole)

OR

CYP 1A2 ultra-rapid metabolizer

+ Inhibitor (Fluoxetine, paroxetine, bupropion, etc)

OR

CYP 1A2 or CYP 2D6 poor metabolizers

++ Inhibitor (ciprofloxacin, fluvoxamine)

OR

Viral or bacterial illness

Meyer, J. M., & Stahl, S. M. (2019). *The Clozapine Handbook: Stahl's Handbooks*: Cambridge University Press.

Infection and clozapine levels

- Infection → inflammation → increased IL-6, TNF-α, IFNγ → inhibited CYP1A2 → elevated clozapine levels
- Look for an MR ratio >3
- In a systematic review, 40 cases documented signs of elevated clozapine levels in the course of infection
  - 30% without fever, 25% without WBC elevation

Tio N, Schulte PFJ, Martens HJM: Clozapine Intoxication in COVID-19. American Journal of Psychiatry 178:123-127, 2021
Clark, S. R., Warren, N. S., Kim, G., Jankowiak, D., Schubert, K. O., Kisely, S., . . . Siskind, D. J. (2018). Elevated clozapine levels associated with infection: A systematic review. *Schizophr Res, 192*, 50-56. doi:10.1016/j.schres.2017.03.045

Individuals of Asian Ancestry and Clozapine

- Ancestral origins range from Pakistan to Japan
- Systematic review found clozapine concentration-dose ratio was 1.57 in East Asians versus 1.07 in Caucasians
- Authors suggested Asian patients need about half of the clozapine dose prescribed to Caucasian patients
- Asian patients with average metabolism
  - 150 mg/d female non-smokers
  - 300 mg/d male non-smokers
- Clinical implication: Consider slow titrations

- Ruan, C.-J., Zang, Y.-N., Wang, C.-Y., Cheng, Y.-H., Sun, C., Spina, E., & de Leon, J. (2019). Clozapine Metabolism in East Asians and Caucasians: A Pilot Exploration of the Prevalence of Poor Metabolizers and a Systematic Review. *Journal of Clinical Psychopharmacology, 39*(2); de Leon, J., Rajkumar, A. P., Kaithi, A. R., Schoretsanitis, G., Kane, J. M., Wang, C. Y., . . . Andrade, C. (2020). Do Asian Patients Require Only Half of the Clozapine Dose Prescribed for Caucasians? A Critical Overview. *Indian journal of psychological medicine, 42*(1), 4-10.

Patients of Asian Ancestry (Average Clozapine Metabolism)

- Week 1: 12.5 mg at night, then increasing by 12.5 mg per day. Target 50 mg/day
- Week 2: Increase by 12.5 mg/day. Target 100 mg/day
  - **After week 3, get a plasma clozapine level!**
- Week 3: Increase by 25 mg/day assuming tolerability. Target 150 mg/day
  - Future titration based on results of the plasma level, if needed repeat level with frequency based on clinical need

de Leon J, Schoretsanitis G, Smith RL, Molden E, Solismaa A, Seppälä N, Kopeček M, Švancer P, Olmos I, Ricciardi C, Iglesias-Garcia C, Iglesias-Alonso A, Spina E, Ruan CJ, Wang CY, Wang G, Tang YL, Lin SK, Lane HY, Kim YS, Kim SH, Rajkumar AP, González-Esquivel DF, Jung-Cook H, Baptista T, Rohde C, Nielsen J, Verdoux H, Quiles C, Sanz EJ, De Las Cuevas C, Cohen D, Schulte PFJ, Ertuğrul A, Anıl Yağcıoğlu AE, Chopra N, McCollum B, Shelton C, Cotes RO, Kaithi AR, Kane JM, Farooq S, Ng CH, Bilbily J, Hiemke C, López-Jaramillo C, McGrane I, Lana F, Eap CB, Arrojo-Romero M, Rădulescu F, Seifritz E, Every-Palmer S, Bousman CA, Bebawi E, Bhattacharya R, Kelly DL, Otsuka Y, Lazary J, Torres R, Yecora A, Motuca M, Chan SKW, Zolezzi M, Ouanes S, De Berardis D, Grover S, Procyshyn RM, Adebayo RA, Kirilochev OO, Soloviev A, Fountoulakis KN, Wilkowska A, Cubała WJ, Ayub M, Silva A, Bonelli RM, Villagrán-Moreno JM, Crespo-Facorro B, Temmingh H, Decloedt E, Pedro MR, Takeuchi H, Tsukahara M, Gründer G, Sagud M, Celofiga A, Ignjatovic Ristic D, Ortiz BB, Elkis H, Pacheco Palha AJ, A LL, Fernandez-Egea E, Siskind D, Weizman A, Masmoudi R, Mohd Saffian S, Leung JG, Buckley PF, Marder SR, Citrome L, Freudenreich O, Correll CU, Müller DJ. An International Adult Guideline for Making Clozapine Titration Safer by Using Six Ancestry-Based Personalized Dosing Titrations, CRP, and Clozapine Levels. Pharmacopsychiatry. 2021. Epub 2021/12/16. doi: 10.1055/a1625-6388. PubMed PMID: 34911124.

Two Methods to Obtain Levels

LC-MS/MS

- Expected Turnaround Time: 2 - 5 days
  - Confirmatory or additional reflex test can extend time
  - Testing schedules may vary
- Generally - have to send off site
- Minimum volume 0.3 - 1 mL
- Results are given with reference ranges all over the board
- No FDA approval or guidance on equipment or assay for clozapine
- Estimated costs $35-$120

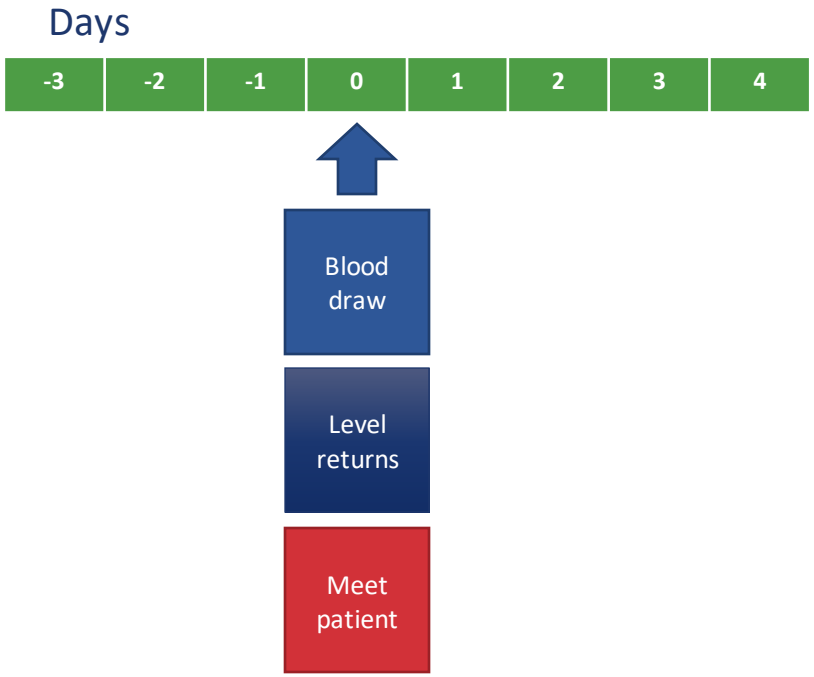
Immunoassay

- < 30 minutes to generate result
- Testing can be STAT
- Can run on-site
- Minimum volume - .2 mL
- FDA cleared assay
- Cost: average cost $19.75*
- Limitation: No norclozapine levels

* Site dependent

Advantages of same-day clozapine levels

1. Can make urgent patient care decisions about adjusting dose, particularly important in Emergency Room settings
2. Improved workflow
3. Improved collaboration between prescribers and patients



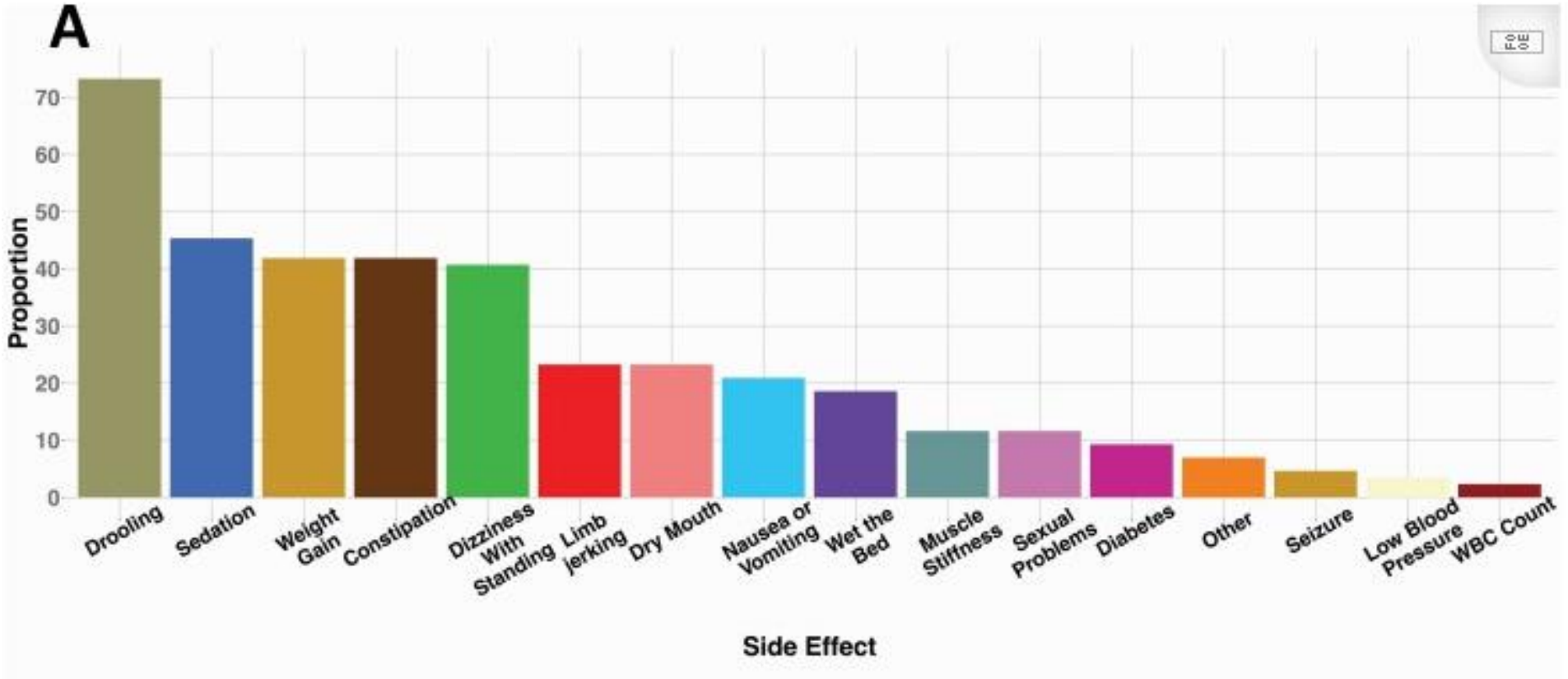
LAI TDM: Obtain 1h – 72 hours prior to next injection

Antipsychotic	AGNP/ASCP Rec Level (oral)	Therapeutic Threshold (ng/ml)	Point of Futility (ng/ml)	AGNP/ASCP Lab Alert Level (ng/ml)	Oral Concentration/ Dose Relationship
Aripiprazole	Recommended	110	500	1000	11.7
Fluphenazine	Strongly recommended	1.0	4.0	15	Smoker: 0.06 Nonsmoker: 0.08 to 0.10
Haloperidol	Strongly recommended	2.0	18	15	0.78
Olanzapine	Strongly recommended	23	150	100	Smoker: 1.43 Nonsmoker: 2.0
Paliperidone	Recommended	20	90	120	4.09
Risperidone (active moiety)	Recommended	15	112	120	**7.0**

Schoretsanitis G, et al. J Clin Psych 2020;81(3):doi: 10.4088/JCP.4019cs13169.Meyer JM and Stahl SM. The Clinical Use of Antipsychotic Plasma Levels (Stahl's Handbooks). Cambridge Univ. Press, 2021; 382 pp.

Managing Clozapine SE

Side Effect Distribution



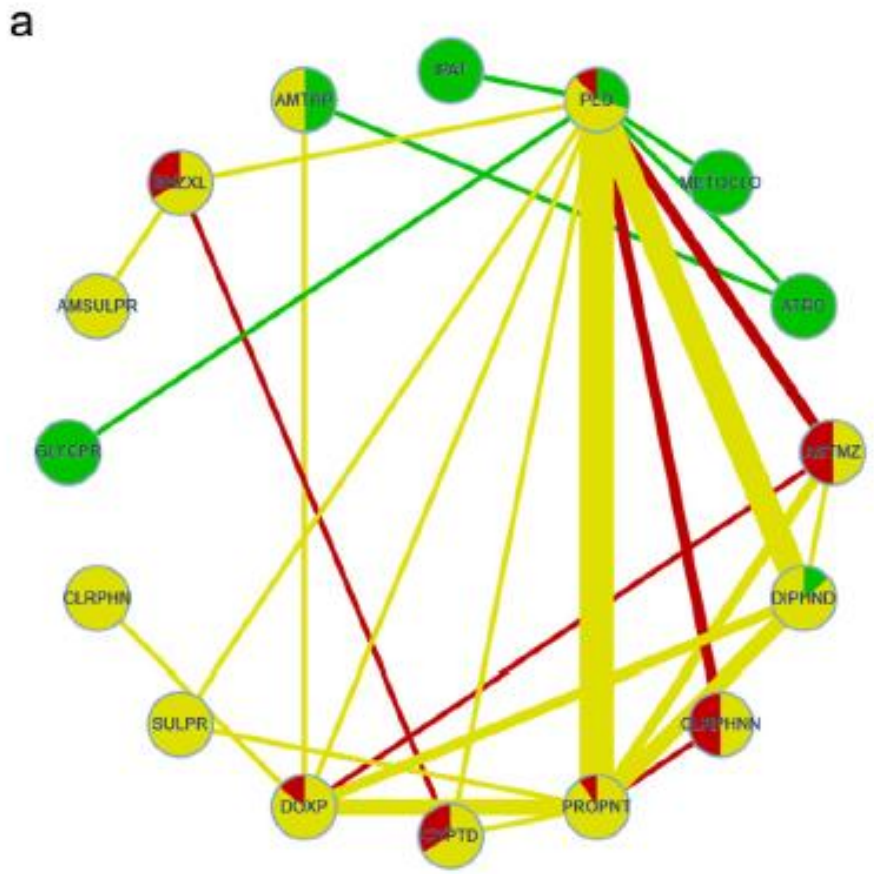
Sharma, S., Kopelovich, S. L., Janjua, A. U., Pritchett, C., Broussard, B., Dhir, M., . . . Cotes, R. O. (2021). Cluster Analysis of Clozapine Consumer Perspectives and Comparison to Consumers on Other Antipsychotics. *Schizophr Bull Open, 2*(1), sgab043.

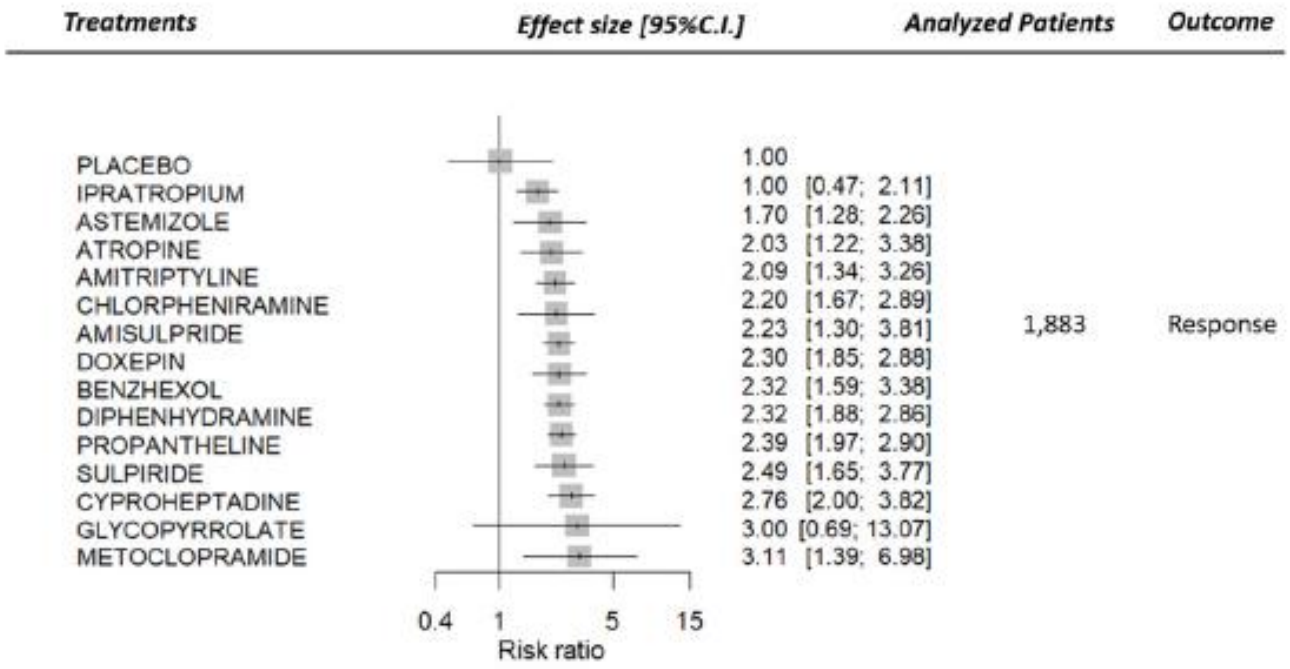
Sialorrhea

Drug	Mechanism	Administration	Dosage Range
First-line treatments			
Atropine 1% ophthalmic solution	Locally acting muscarinic antagonist	Sublingual drops OR swish and spit	1 drop qhs-3 drops TID
Ipratropium bromide 0.06% nasal spray	Locally acting muscarinic antagonist	Swish and spit OR spray under tongue	1-3 drops intraorally qhs
Second-line treatments			
Clonidine	Alpha$_2$ adrenergic agonist	PO OR transdermal patch	0.05-0.1 mg/day
Botulinum toxin-B injections	Diminishes release of synaptic acetylcholine	Parotid and submandibular gland injections	Injections every 4-6 mo
Glycopyrrolate	Nonselective muscarinic antagonist	PO	1-8 mg total daily, either qhs or BID; monitor for constipation

Meyer. The Clozapine Handbook. 2019.

Wait…what should we do with this?





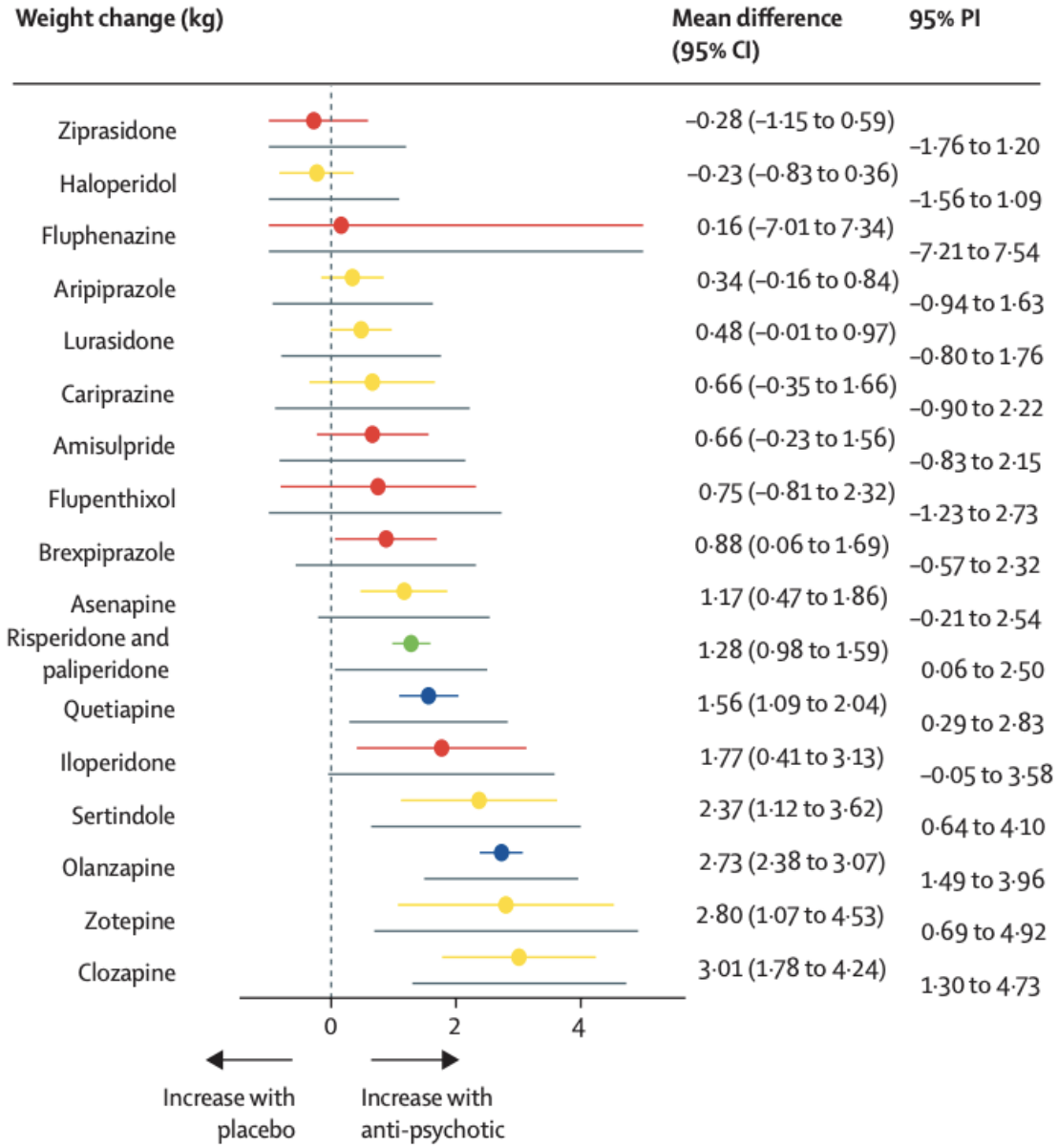
Fornaro M, Caiazza C, Solini N, et al: Pharmacological interventions for antipsychotic-related sialorrhea: a systematic review and network meta-analysis of randomized trials. Molecular Psychiatry, 2023

Sialorrhea resources

https://smiadviser.org/knowledge_post/sialorrhea-treatment

Clozapine has the highest cardiometabolic liability

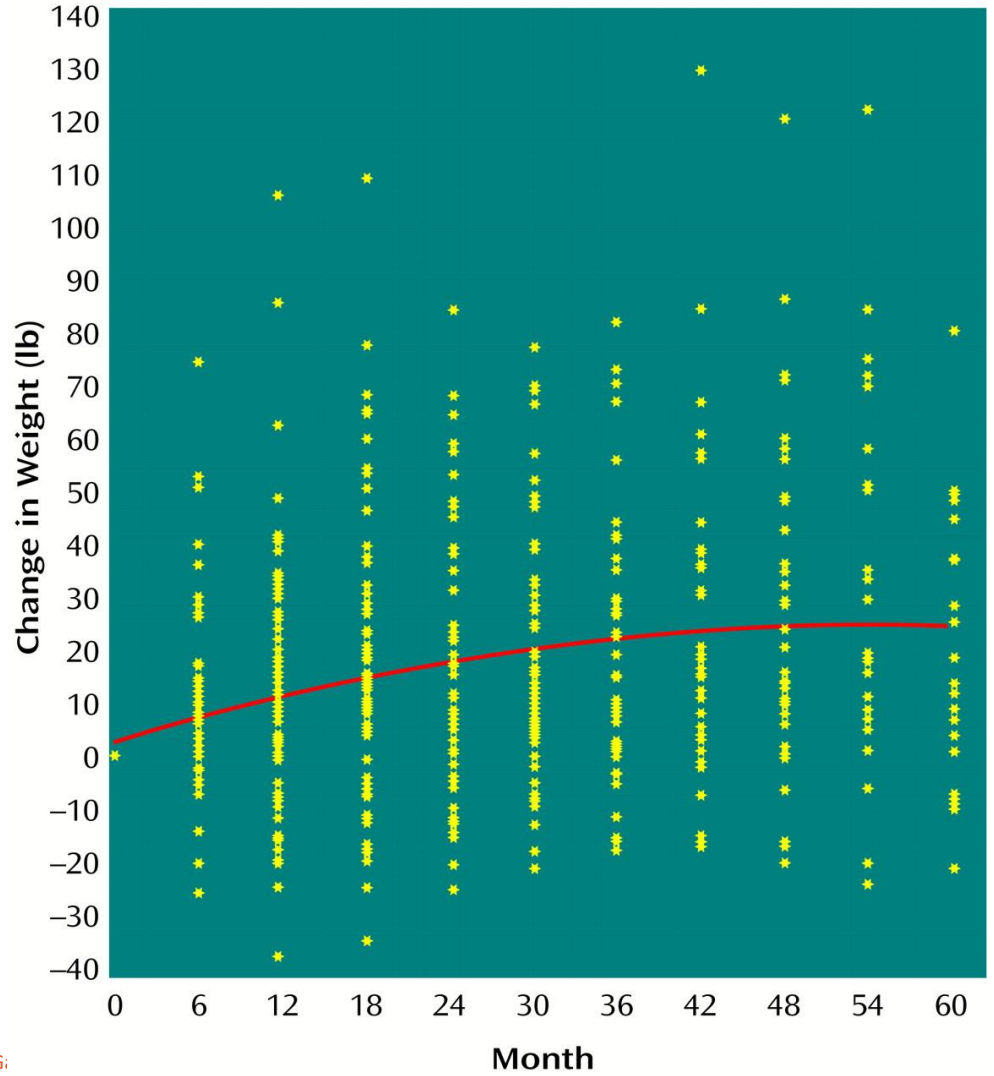
- In a comparative meta-analysis including 18 antipsychotics:
  - Clozapine caused the greatest amount of weight gain, glucose alteration, and triglyceride change
  - Predictors of AIWG included increased baseline body weight, male sex, and non-white ethnicity.



Pillinger, T., McCutcheon, R. A., Vano, L., Mizuno, Y., Arumuham, A., Hindley, G., . . . Howes, O. D. (2020). Comparative effects of 18 antipsychotics on metabolic function in patients with schizophrenia, predictors of metabolic dysregulation, and association with psychopathology: a systematic review and network meta-analysis. *The Lancet Psychiatry, 7*(1), 64-77. doi:10.1016/S2215-0366(19)30416-X

Clozapine and cardiometabolic SE

- Five-year naturalistic study (N=82)
  - Weight gain finally plateaued at 4th year
  - 37% developed diabetes
- Weight gain, triglycerides, and total cholesterol may correlate with increasing norclozapine levels
- Some suggestion that the ideal MR ratio may be 2 (better cardiometabolic outcomes and possibly cognition) though further studies are needed



Henderson, D. C., Cagliero, E., Gray, C., Nasrallah, R. A., Hayden, D. L., Schoenfeld, D. A., & Goff, D. C. (2000). Clozapine, Diabetes Mellitus, Weight G
975-981. doi:10.1176/appi.ajp.157.6.975. Tan, M. S. A., Honarparvar, F., Falconer, J. R., Parekh, H. S., Pandey, P., & Siskind, D. J. (2021). A systematic review and meta-analysis of the association between clozapine and norclozapine serum levels and peripheral adverse drug reactions. *Psychopharmacology (Berl)*. doi:10.1007/s00213-020-05746-y Costa-Dookhan KA, Agarwal SM, Chintoh A, Tran VN, Stogios N, Ebdrup BH, Sockalingam S, Rajji TK, Remington GJ, Siskind D, Hahn MK. The clozapine to norclozapine ratio: a narrative review of the clinical utility to minimize metabolic risk and enhance clozapine efficacy. Expert Opin Drug Saf. 2020 Jan;19(1):43-57. doi: 10.1080/14740338.2020.1698545. Epub 2019 Dec 2. PMID: 31770500.

Management of AIWG

- Taper/discontinue other contributors
- Exceed minimum thresholds established by APA/ADA guidelines
- Majority of early weight gain occurs at 4-6 weeks so act quickly
- Weight gain primarily due to H_1 antagonism causing increased appetite, limited data on if the effect is dose dependent
- Heavy emphasis on physical activity, lifestyle programs, and diet modification
- Consider prophylactic metformin (-3.12 kg v PBO in clozapine-treated patients)
  - **Titration:** Start at 500 mg w/dinner, increase to 500 mg BID (with meals) **after 2–3 weeks** to minimize GI SEs, and then by 500 mg/wk until 1000 mg BID. Use extended-release form if GI SEs develop (e.g., diarrhea)
  - Clozapine-treated patients prophylactically started on metformin were more likely to stay on clozapine at 12 months in one study (Stogios et al., 2022)

Siskind, D. J., Leung, J., Russell, A. W., Wysoczanski, D., & Kisely, S. (2016). Metformin for Clozapine Associated Obesity: A Systematic Review and Meta-Analysis. *PLoS One, 11*(6), e0156208. doi:10.1371/journal.pone.0156208; Stogios N, Maksyutynska K, Navagnanavel J, et al: Metformin for the prevention of clozapine-induced weight gain: A retrospective naturalistic cohort study. Acta Psychiatrica Scandinavica 146:190-200, 2022

GLP-1 agonists

- **GLP-1 agonists (e.g., exenatide SC, liraglutide SC, semaglutide PO):** GLP-1 is secreted by L cells in GI mucosa in response to a meal. GLP-1 slows gastric emptying, increases insulin secretion by β-cells, & decreases glucagon secretion by inhibiting pancreatic α-cells.
  - Administration: SC injection, newer forms have q week dosing. **Semaglutide** is now available in an oral form.
  - Benefits: **weight loss** in addition to impact on glycemic parameters (e.g. A1C). Studied in pts on olanzapine or clozapine, and wt loss vs PBO over 16 wks averaged 3.71 kg ($p < 0.001$). **NNT for ≥ 5% body weight loss = 4**
  - **Common adverse effects:** Predominantly GI (n/v, diarrhea or constipation, cholelithiasis (possibly due to wt loss)). Hypoglycemia not an issue unless used with insulin or sulfonylureas. Unclear risk of pancreatitis or medullary thyroid cancer.
  - **Issue:** Expensive, in high demand and indications are typically limited to type 2 DM or obesity/overweight

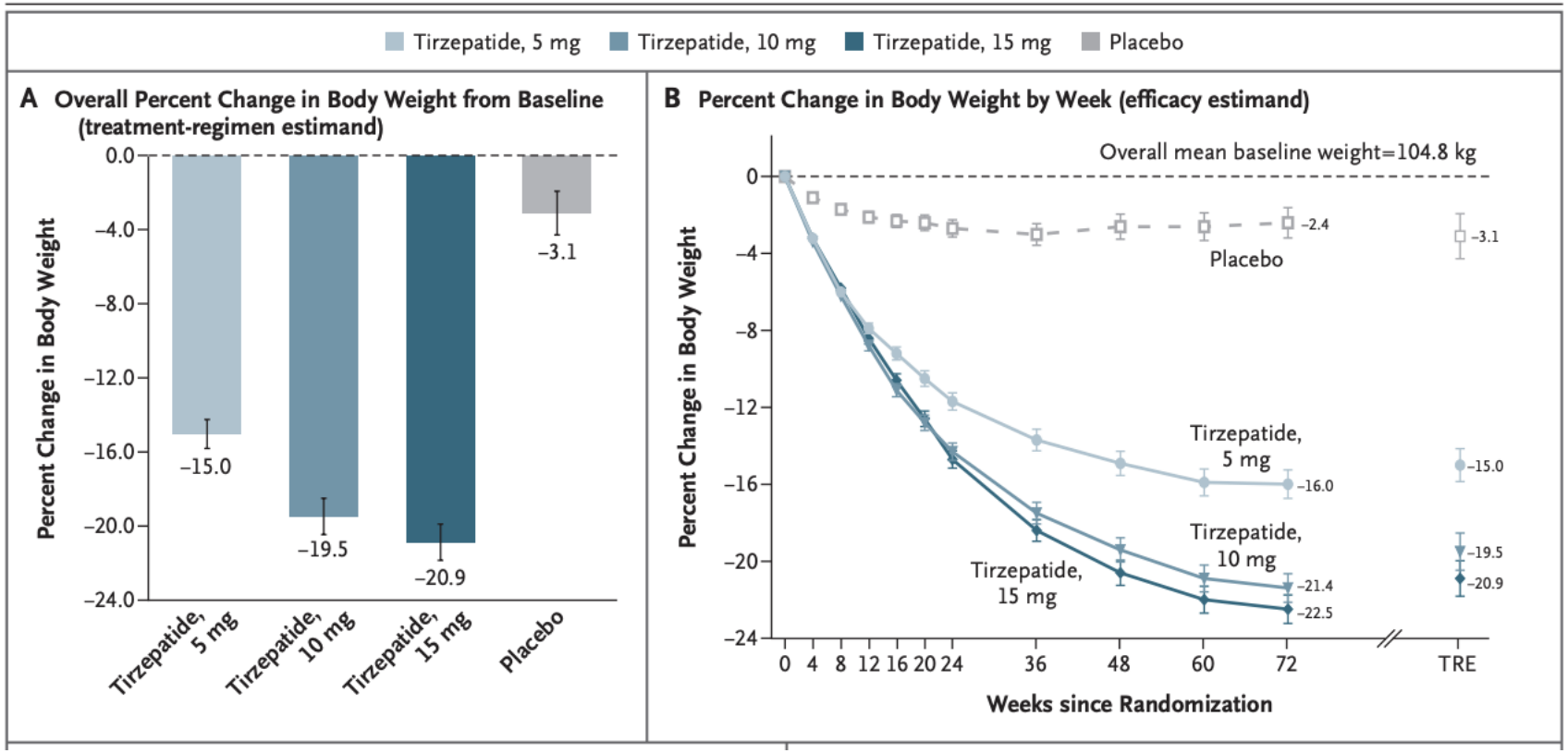
Currently Available GLP-1 and GIP RAs

Drug	Brand Name	Dose	Route	Frequency	Indication
Exenatide	Byetta®	5-10 mg	SQ	BID	Diabetes
Exenatide ER	Bydureon BCise®	2 mg	SQ	Weekly	Diabetes
Liraglutide	Victoza®	0.6-1.8 mg	SQ	Daily	Diabetes
	Saxenda®	**0.6-3 mg**	**SQ**	**Daily**	**Weight Loss**
Dulaglutide	Trulicity®	0.75-4.5 mg	SQ	Weekly	Diabetes
Semaglutide	Ozempic®	0.25-2 mg	SQ	Weekly	Diabetes
	Rybelsus®	3-14 mg	PO	Daily	Diabetes
	Wegovy®	**0.25-2.4 mg**	**SQ**	**Weekly**	**Weight Loss**
Tirzepatide	Mounjaro®	2.5 – 15 mg	SQ	Weekly	Diabetes
Tirzepatide	Zepbound®	2.5 -15 mg	SQ	**Weekly**	**Weight Loss**

Adapted from Dr. Kristi Haman, PharmD, Grady Health System

Tirzepatide

- Agonist at GIP and GLP-1
- SURMOUNT-1 trial included N=2539 participants
- AEs (mostly GI) led to discontinuation in 4.3-7.1% of participants
- FDA approved for adults with obesity or overweight with weight related condition in Nov 2023
- Not systematically studied for clozapine (yet)



Jastreboff, A. M., Aronne, L. J., Ahmad, N. N., Wharton, S., Connery, L., Alves, B., . . . Stefanski, A. (2022). Tirzepatide Once Weekly for the Treatment of Obesity. *N Engl J Med, 387*(3), 205-216. doi:10.1056/NEJMoa2206038

Clozapine, GLP-1 RA's, and gastroparesis

- Gastroparesis sx include n/v, abdominal pain, early satiety, abdominal fullness, bloating
- Gastric emptying was delayed in 41% of participants on clozapine (small study, 17 total)
- Tx options include metoclopramide, plucalopride, and domperidone

Table 1. Characteristics of Semaglutide, Liraglutide, and Bupropion-Naltrexone Users

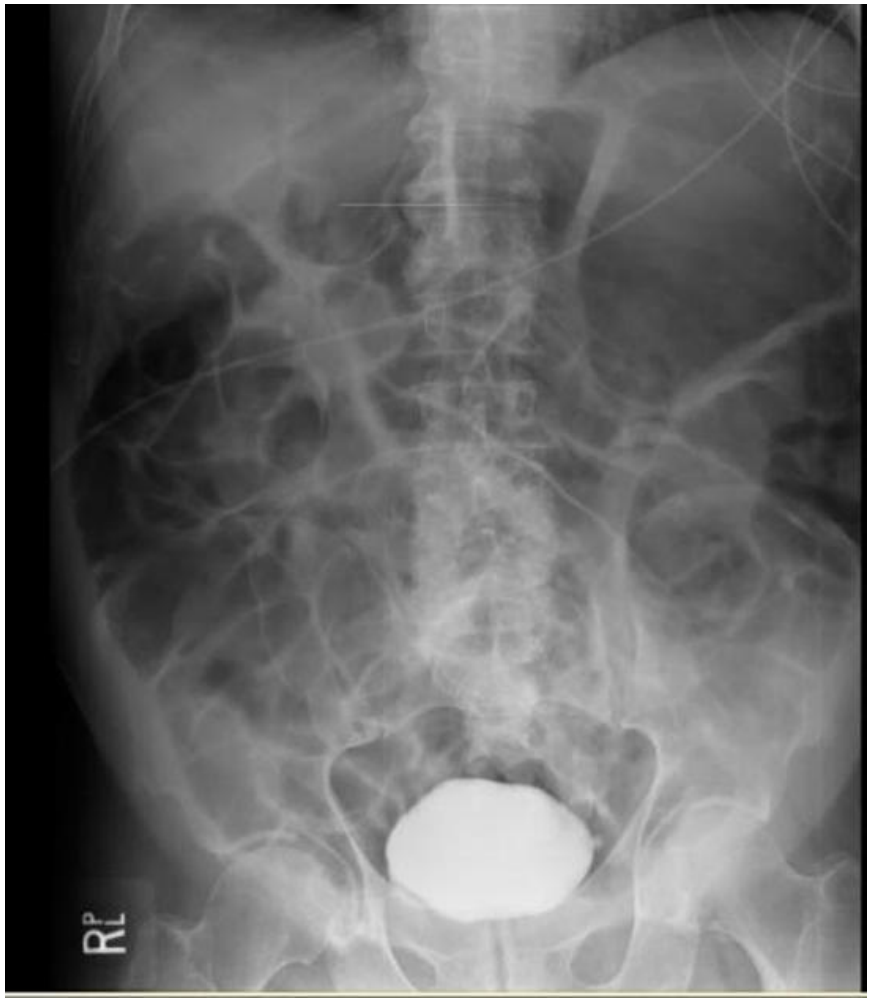
	Semaglutide	Liraglutide	Bupropion-naltrexone
No.	613	4144	654
Age, mean (SD), y	53.5 (11.9)	51.3 (12.2)	45.2 (11.1)
Sex, %			
Male	55.8	61.0	82.4
Female	44.2	39.0	17.6
Follow-up, median (IQR), y	0.6 (0.2-1.1)	1.7 (0.8-3.1)	1.7 (0.7-2.9)
Covariates, %			
Alcohol[a]	2.9	0.4	0.6
Smoking[a]	8.7	12.5	9.9
Hyperlipidemia[b]	55.6	22.8	11.5
Abdominal surgery[c]	0	0.12	0
US region			
Northeast	18.3	25.8	18.3
Southeast	34.6	26.1	34.6
Midwest	33.1	30.3	33.1
Southwest	0.2	2.6	0.3
West	13.9	15.3	12.4
Incidence (No.)[d]			
Biliary disease	11.7 (5)	18.6 (162)	12.6 (16)
Pancreatitis	4.6 (2)	7.9 (71)	1.0 (1)
Bowel obstruction	0	8.1 (73)	1.7 (2)
Gastroparesis	9.1 (4)	7.3 (66)	3.1 (3)

Sodhi M, Rezaeianzadeh R, Kezouh A, Etminan M: Risk of Gastrointestinal Adverse Events Associated With Glucagon-Like Peptide-1 Receptor Agonists for Weight Loss. JAMA, 2023; Every-Palmer S, Inns SJ, Grant E, Ellis PM: Effects of Clozapine on the Gut: Cross-Sectional Study of Delayed Gastric Emptying and Small and Large Intestinal Dysmotility. CNS Drugs 33:81-91, 2019

Constipation

- Colonic transit time study:
  - Not prescribed clozapine n=17, CTT 23 h
  - Prescribed clozapine, n=20, CTT 104.5 h
- Ileus
  - May occur with prolonged exposure in a level-dependent fashion
    - Median time to developing ileus was 1528 days
  - Clozapine associated with a 2X risk of ileus, 7X risk of fatal ileus

https://radiopaedia.org/articles/adynamic-ileus



Every-Palmer S, Nowitz M, Stanley J, Grant E, Huthwaite M, Dunn H, Ellis PM. Clozapine-treated Patients Have Marked Gastrointestinal Hypomotility, the Probable Basis of Life-threatening Gastrointestinal Complications: A Cross Sectional Study. EBioMedicine. 2016 Mar;5:125-34. PMID: 27532076.

Nielsen J, Meyer JM. Risk factors for ileus in patients with schizophrenia. Schizophr Bull. 2012 May;38(3):592-8. doi: 10.1093/schbul/sbq137. Epub 2010 Nov 26. PMID: 21112965; PMCID: PMC3329981.

Constipation

- Prevention
  - Reduce opioids, iron (if not needed) and anticholinergics
  - Encourage activity
  - Hydration
  - Avoid bulk laxatives like psyllium
- Education
  - Educate staff, family, patient!!
  - Have patients tell you if the frequency of bowel movements changes

Shirazi, A., Stubbs, B., Gomez, L., Moore, S., Gaughran, F., Flanagan, R. J., . . . Lally, J. (2016). Prevalence and Predictors of Clozapine-Associated Constipation: A Systematic Review and Meta-Analysis. *International journal of molecular sciences, 17*(6), 863.

Every-Palmer, S., Ellis, P. M., Nowitz, M., Stanley, J., Grant, E., Huthwaite, M., & Dunn, H. (2017). The Porirua Protocol in the Treatment of Clozapine-Induced Gastrointestinal Hypomotility and Constipation: A Pre- and Post-Treatment Study. *CNS Drugs, 31*(1), 75-85.

Recommended Bowel Regimen

1. Prophylactic docusate 250 mg BID with rescue PRN
   - PRN: magnesium citrate 150 mL or magnesium hydroxide 30 mL every 2 days without BM
2. Add one osmotic laxative
   - Example: polyethylene glycol 17 g qam
3. Add one stimulant laxative
   - Example: sennosides 17.2 mg (max 34.4 mg BID) or bisacodyl starting at 5 mg qhs (max 30 mg per day)
4. Add a secretagogue with consideration of tapering other agents
   - Example: linaclotide, lubiprostone

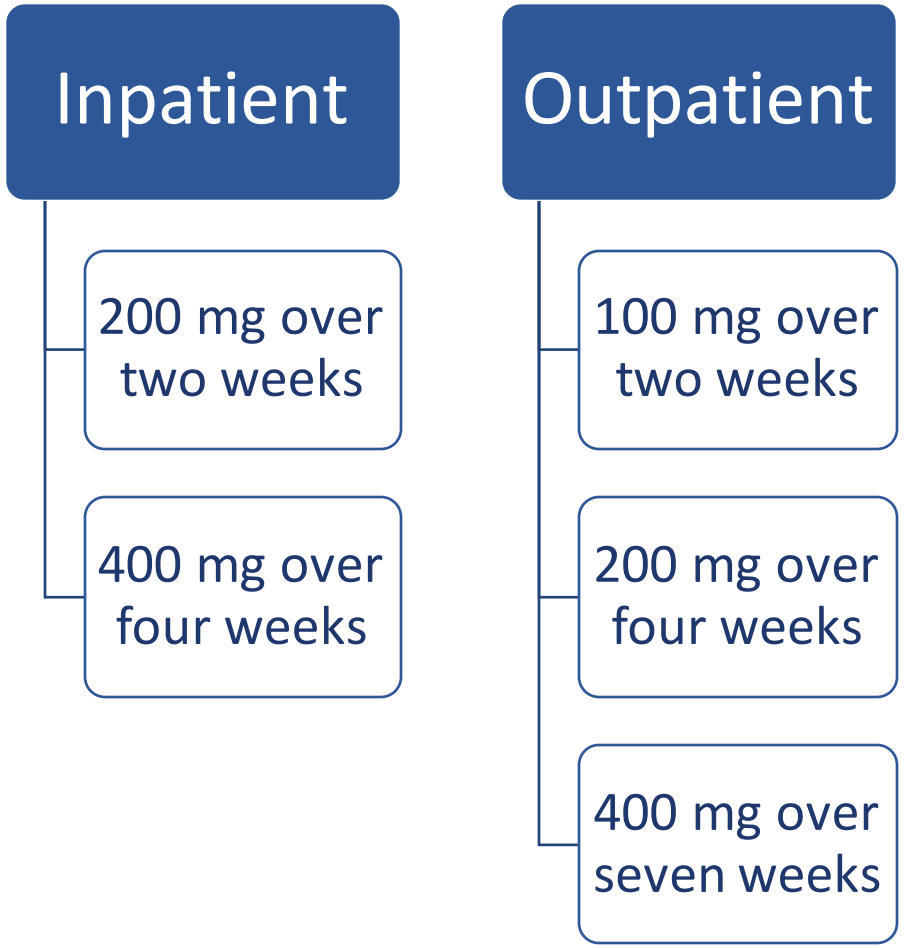
Constipation Management Protocol for Clozapine Treated Patients. California Department of State Hospitals. 2020. Used with permission from Dr. Jonathan Meyer.

Myocarditis

- Mechanism: unclear, IgE hypersensitivity reaction, increased cytokines release
- Incidence varies, largest meta-analysis 0.7%
- Mean time until onset 17 days, 82% occurring between days 14-21
- Known associations: sodium valproate, age, rapid clozapine titrations
- Non-specific symptoms: fever, fatigue, flu-like symptoms, chest pain, tachycardia, palpitations, hypotension, dyspnea, signs of heart failure, electrocardiographic changes
- Screening protocol: weekly CRP, troponin I/T for first 6 weeks
- Management: discontinue clozapine and obtain cardiac evaluation (EKG, TTE, cardiac MRI). Have been successful rechallenges.

Siskind, D., Sidhu, A., Cross, J., Chua, Y. T., Myles, N., Cohen, D., & Kisely, S. (2020). Systematic review and meta-analysis of rates of clozapine-associated myocarditis and cardiomyopathy. *Aust N Z J Psychiatry, 54*(5), 467-481. doi:10.1177/0004867419898760. Ronaldson, K. J., Fitzgerald, P. B., Taylor, A. J., Topliss, D. J., & McNeil, J. J. (2011). A new monitoring protocol for clozapine-induced myocarditis based on an analysis of 75 cases and 94 controls. *Aust N Z J Psychiatry, 45*(6), 458-465. Ronaldson, K. J., Fitzgerald, P. B., Taylor, A. J., Topliss, D. J., Wolfe, R., & McNeil, J. J. (2012). Rapid clozapine dose titration and concomitant sodium valproate increase the risk of myocarditis with clozapine: a case-control study. *Schizophr Res, 141*(2-3), 173-178. Cook, S. C., Ferguson, B. A., Cotes, R. O., Heinrich, T. W., & Schwartz, A. C. (2015). Clozapine-Induced Myocarditis: Prevention and Considerations in Rechallenge. *Psychosomatics, 56*(6), 685-690.

Relatively slow, individualized titration



- USPI may be too quick (up to 300-450 mg per day after 2 weeks)
- More rapid titrations possibly associated with myocarditis risk (Ronaldson et al. 2012)
- Early tolerability issues may lead to self-discontinuation
- Therapeutic drug monitoring can be helpful
- Plan out how you want to execute the cross-taper with the other antipsychotic(s)

Managing Missed Doses

Updated US Package Insert Language on Missed Doses for Clozapine

"If one day's dosing has been missed, resume treatment at 40% to 50% of the established dose. If two days dosing have been missed, resume dose at approximately 25% of the established dosage. For longer interruptions, re-initiate at a dosage of 12.5 mg once daily or twice daily. If these dosages are well-tolerated, the dosage may be increased to the previous dosage more quickly than recommended for initial treatment."

Source: HLS Therapeutics. (2023). Clozapine Prescribing Information.
https://www.hlstherapeutics.com/wp-content/uploads/monograph_pdf/HLS-Clozaril-PM-US.pdf

Alternate Strategy (Not Evidence-Based; Caution)

- 1-2 days: restart dose
- 3-7 days:
  - X = (original dose in mg)/(N days missed)
  - Day 1 dose is X, Day 2 dose is 2X, and so forth until previous dose is reached
- > 7 days consider restarting at 25 mg
- Consider smoking status and presence/absence of other inducers.

Challenges

Combining LAIs?

- Limited evidence but similar considerations for antipsychotic polypharmacy
- 9 case reports summarized in 2021
- Retrospective, mirror-image study 13 TRS patients showed decreased number of hospitalizations
- May encounter challenges with insurance coverage

Evernden C, Giang I, Anderson M: The use of concurrent long-acting injectable antipsychotic therapy with paliperidone palmitate and aripiprazole monohydrate in a patient with schizophrenia. Ment Health Clin 11:305-310, 2021; Calvin N, Minischetti L, Salanon F, et al: Combination of two long-acting injectable antipsychotics in treatment-resistant schizophrenia: A retrospective 12-month mirror-image study. Asian Journal of Psychiatry 80:103402, 2023

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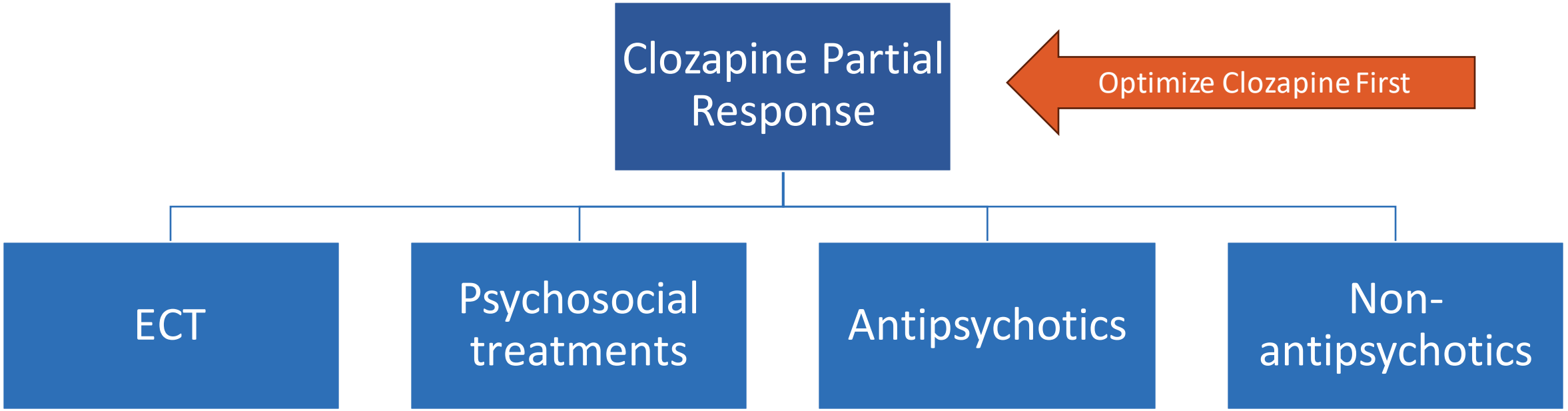
Clozapine Response Rates

- Meta-analysis of 21 studies
- 40% response rate to clozapine
  - Mean PANSS reduction 22 points (25.8% from baseline)
  - 32% in the short-term
  - 39% in the long-term
- Suggests 12% to 20% of people with SCZ are clozapine-resistant

Siskind, D., Siskind, V., & Kisely, S. (2017). Clozapine Response Rates among People with Treatment-Resistant Schizophrenia: Data from a Systematic Review and Meta-Analysis. *Can J Psychiatry, 62*(11), 772-777.

Augmentation Options



TRRIP Consensus Guidelines

- Recommendations which reached ≥75% agreement for refractory positive symptoms
  - Raise clozapine plasma levels to ≥ 350 ng/ml
  - Wait for a delayed response at an adequate dose (mean 15 wks, median 12 wks)
  - Combine with second antipsychotic (aripiprazole, amisulpride)
  - Augment with ECT
  - CBT
  - Psychosocial interventions

Wagner E, Kane JM, Correll CU, Howes O, Siskind D, Honer WG, Lee J, Falkai P, Schneider-Axmann T, Hasan A; TRRIP Working Group. Clozapine Combination and Augmentation Strategies in Patients With Schizophrenia -Recommendations From an International Expert Survey Among the Treatment Response and Resistance in Psychosis (TRRIP) Working Group. Schizophr Bull. 2020 Dec 1;46(6):1459-1470. doi: 10.1093/schbul/sbaa060. PMID: 32421188; PMCID: PMC7846085.

Clozapine therapeutic threshold

- AGNP guidelines reference range 350 – 600 ng/mL
- Risk of ADRs increase at levels above 1000 ng/mL
- Other sources indicate levels up to 1000 are not unsafe and should be pursued in non-responders
  - In a cross-sectional study of 131 patients with TRS on clozapine, every 100 ng/ml increase in plasma clozapine levels resulted in an improved BPRS score of 2%. Concentrations in the 600-1000 ng/mL range were more effective than those in the 350-600 ng/mL range

Rostami-Hodjegan, A., Amin, A. M., Spencer, E. P., Lennard, M. S., Tucker, G. T., & Flanagan, R. J. (2004). Influence of dose, cigarette smoking, age, sex, and metabolic activity on plasma clozapine concentrations: a predictive model and nomograms to aid clozapine dose adjustment and to assess compliance in individual patients. *J Clin Psychopharmacol, 24*(1), 70-78. doi:10.1097/01.jcp.0000106221.36344.4d. Yada Y, Kitagawa K, Sakamoto S, et al: The relationship between plasma clozapine concentration and clinical outcome: a cross-sectional study. Acta Psychiatr Scand 143:227-237, 2021

Clozapine and ECT

- Petrides et al., 2015
  - Single-blind 8 week randomized to TAU or BL ECT, non-responders received 8-week open ECT trial
  - Response defined as ≥40% reduction in psychotic sx subscale of BPRS, CGI <3, CGI-I ≤2
  - 50% ECT + clozapine group, 47% crossover phase. No change in cognition
- Melzer-Ribeiro et al., 2023
  - Double-blind RCT comparing ECT (n=21) to sham-ECT (n=19)
  - 20 sessions of bitemporal ECT administered twice weekly
  - Average clozapine level 909 ng/mL
  - 1/19 ECT completers and 0/17 sham-ECT completers responded (defined by ≥50% reduction in PANSS score

Petrides, G., Malur, C., Braga, R. J., Bailine, S. H., Schooler, N. R., Malhotra, A. K., . . . Mendelowitz, A. (2015). Electroconvulsive therapy augmentation in clozapine-resistant schizophrenia: a prospective, randomized study. *Am J Psychiatry, 172*(1), 52-58. Melzer-Ribeiro DL, Napolitano IC, Leite SA, et al: Randomized, double-blind, sham-controlled trial to evaluate the efficacy and tolerability of electroconvulsive therapy in patients with clozapine-resistant schizophrenia. Schizophrenia Research, 2023

Rehospitalization data

- Finish nation-wide cohort study using a within-individual analysis
- N = 62,250 patients
- Lowest rates of rehospitalization (HR)
  - Clozapine + aripiprazole (0.42)
  - Any LAI and olanzapine (0.48)
  - Clozapine + olanzapine (0.49)
  - Clozapine monotherapy (0.49)
  - Clozapine + any LAI (0.50)

Tiihonen, J., Taipale, H., Mehtala, J., Vattulainen, P., Correll, C. U., & Tanskanen, A. (2019). Association of Antipsychotic Polypharmacy vs Monotherapy With Psychiatric Rehospitalization Among Adults With Schizophrenia. *JAMA Psychiatry*.

Clozapine and LAIs

- Systematic review of 12 articles including 195 patients with all studies reporting a favorable outcome, despite different outcome measures used
- LAIs may have a theoretical benefit during periods of clozapine non-adherence
- No clear explanation for why LAIs would be more effective than orals if both taken consistently

Oloyede E, Dima A, Taylor D, Cheung H, Dzahini O, Shergill S, Whiskey E. Clozapine augmentation with long-acting antipsychotic injections: A case series and systematic review. Acta Psychiatr Scand. 2023 Dec;148(6):538-552. doi: 10.1111/acps.13621. Epub 2023 Oct 29. PMID: 37899506.

Non-antipsychotic augmentation options

Option	Notes
Famotidine	1 RCT (Meskanen et al., 11/30 on clozapine), improved positive and general sx
Gingko biloba	1 RCT (Doruk et al.) 42 patients, decreased NS (not positive nor overall)
Lamotrigine	Potential role, may reduce alcohol use, mixed evidence and two outlying studies
Memantine	2 RCTs show benefit in positive, negative, and cognitive sx
Minocycline	8 PBO-controlled studies. “Probably not effective” – Maudsley handbook
Mirtazapine	1 RCT (Zoccali et al.) benefit for negative sx
Omega-3 triglycerides	“Modest, and somewhat contested evidence” -Maudsley handbook
Pimavanserin	1 case series (Nasrallah et al., N=6) improvement in positive sx
Topiramate	5 RCT some improvement in positive sx and general psychopathology
Sodium benzoate	1 RCT (Lin et al.) improved positive and negative sx
Sodium valproate	At least 9 RCTs, small effect on general psychopathology; kinetic interaction, neutropenia

Adapted from Meyer JM, Stahl SM. The Clozapine Handbook: Stahl's Handbooks: Cambridge University Press; 2019. Taylor DM, Barnes TRE, Young AH. The Maudsley Prescribing Guidelines in Psychiatry: Wiley; 2021.

Question and Answer

AMERICAN PSYCHIATRIC ASSOCIATION

SAMHSA Substance Abuse and Mental Health Services Administration